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PATENT- OG VAREMÆRKESTYRELSEN

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STABILISED INSULIN PREPARATIONS

FIELD OF THE INVENTION

This invention relates to insulin preparations stabilised by adding ligands for the His^{B10} Zn^{2+} sites of the R-state insulin hexamer, as well as methods for preparation and use of such preparations.

BACKGROUND OF THE INVENTION

Diabetes is a general term for disorders in man having excessive urine excretion as in diabetes mellitus and diabetes insipidus. Diabetes mellitus is a metabolic disorder in which the ability to utilize glucose is partly or completely lost.

Since the discovery of insulin in the 1920's, continuous strides have been made to improve the treatment of diabetes mellitus. To help avoid extreme glycaemia levels, diabetic patients often practice multiple injection therapy, whereby insulin is administered with each meal. Many diabetic patients are treated with multiple daily insulin injections in a regimen comprising one or two daily injections of a protracted insulin composition to cover the basal requirement, supplemented by bolus injections of rapid acting insulin to cover the meal-related requirements.

Insulin compositions having a protracted profile of action are well known in the art. Thus, one main type of such insulin compositions comprises injectable aqueous suspensions of insulin crystals or amorphous insulin. Typically, the insulin in these compositions is provided in the form of protamine insulin, zinc insulin or protamine zinc insulin

Soluble, rapid acting insulin preparations usually comprise insulin, insulin analogue or insulin derivative together with zinc ion, phenolic preservative, isotonicity agent, and a buffer substance. In addition, the preparation may optionally contain some salts and/or surfactants. Such preparations contain insulin in the form of an R-state hexamer.

Insulin Allostery.

The insulin hexamer is an allosteric protein that exhibits both positive and negative cooperativity and half-of-the-sites reactivity in ligand binding. This allosteric behaviour consists of two interrelated allosteric transitions designated L^A_0 and L^B_0, three inter-converting allosteric conformation states (eq. 1),

$$T_6 \overset{L^A_0}{\leftrightarrow} T_3R_3 \overset{L^B_0}{\leftrightarrow} R_6 \qquad (1)$$

designated T_6, T_3R_3, and R_6 and two classes of allosteric ligand binding sites designated as the phenolic pockets and the His^{B10} anion sites. These allosteric sites are associated only with insulin subunits in the R conformation.

Insulin Hexamer Structures and Ligand Binding.

The T- to R-transition of the insulin hexamer involves transformation of the first nine residues of the B chain from an extended conformation in the T-state to an alpha-helical conformation in the R-state. This coil-to-helix transition causes the N-terminal residue, Phe^{B1}, to undergo an ~ 30 Å change in position. This conformational change creates hydrophobic pockets (the phenolic pockets) at the subunit interfaces (three in T_3R_3, and six in R_6), and the new B-chain helices form 3-helix bundles (one in T_3R_3 and two in R_6) with the bundle axis aligned along the hexamer three-fold symmetry axis. The His^{B10} Zn^{2+} in each R_3 unit is forced to change coordination geometry from octahedral to either tetrahedral (monodentate ligands) or pentahedral (bidentate ligands). Formation of the helix bundle creates a narrow hydrophobic tunnel in each R_3 unit that extends from the surface ~12 Å down to the His^{B10} metal ion. This tunnel and the His^{B10} Zn^{2+} ion form the anion binding site. Ligands for the His^{B10} Zn^{2+} sites of the R-state insulin hexamer have been disclosed in US 5830999.

Hexamer Ligand Binding and Stability of Insulin Preparations.

The *in vivo* role of the T to R transition is unknown. However, the addition of allosteric ligands (e.g. phenol and chloride ion) to insulin preparations is widely used. Hexamerization is driven by coordination of Zn^{2+} at the His^{B10} sites to give T_6. Following subcutaneous injection, some dilution of the depot will take place over time and the ligands of soluble hexamers most likely diffuse away from the protein relatively rapidly. This is probably due to one or more phenomena including the binding of Zn^{2+} by surrounding tissue and albumin, the relatively larger space available for diffusion of the hydrophobic phenolic preservatives, and the generally larger diffusion coefficients characteristic of the smaller sized molecules.

Insulin preparations are usually stored for extended periods of time e.g. in vials or cartridges. Furthermore, insulin pumps are becoming more widely used, which places an additional demand on the chemical and physical stability of the insulin preparation due to the elevated temperatures and physical stress these preparations are exposed to. There is thus a need for insulin preparations that are more physically and chemically stable. It has been found that stabilising Zn^{2+}-site ligands may be added to insulin preparations to improve these properties.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical preparations comprising insulin and novel ligands for the His^{B10} Zn^{2+} sites of the R-state insulin hexamer. The resulting preparations have improved physical and chemical stability.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows

DEFINITIONS

The following is a detailed definition of the terms used to describe the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I.

The term "alkyl" as used herein represents a saturated, branched or straight hydrocarbon group having the indicated number of carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "alkylene" as used herein represents a saturated, branched or straight bivalent hydrocarbon group having the indicated number of carbon atoms. Representative examples include, but are not limited to, methylene, 1,2-ethylene, 1,3-propylene, 1,2-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, and the like.

The term "alkenyl" as used herein represents a branched or straight hydrocarbon group having the indicated number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-

pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "alkynyl" as used herein represents a branched or straight hydrocarbon group having the indicated number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "alkoxy" as used herein refers to the radical -O- alkyl, wherein alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "cycloalkyl" as used herein represents a saturated, carbocyclic group having the indicated number of carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "cycloalkenyl" as used herein represents a non-aromatic, carbocyclic group having the indicated number of carbon atoms containing one or two double bonds. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

The term "heterocyclyl" as used herein represents a non-aromatic 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and optionally containing one or two double bonds. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein is intended to include carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, carbocyclic, aromatic ring systems. Representative examples are phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "arylene" as used herein is intended to include divalent, carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, divalent, carbocyclic, aromatic ring systems. Representative examples are phenylene, biphenylylene, naphthylene, anthracenylene, phenanthrenylene, fluorenylene, indenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the ring

systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.
The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.
The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term "heteroaryl" as used herein is intended to include aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.
The term "heteroarylene" as used herein is intended to include divalent, aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furylene, thienylene, pyrrolylene, oxazolylene, thiazolylene, imidazolylene, isoxazolylene, isothiazolylene, 1,2,3-triazolylene, 1,2,4-triazolylene, pyranylene, pyridylene, pyridazinylene, pyrimidinylene, pyrazinylene, 1,2,3-triazinylene, 1,2,4-triazinylene, 1,3,5- triazinylene, 1,2,3-oxadiazolylene, 1,2,4-oxadiazolylene, 1,2,5-oxadiazolylene, 1,3,4-oxadiazolylene, 1,2,3-thiadiazolylene, 1,2,4-thiadiazolylene, 1,2,5-thiadiazolylene, 1,3,4-thiadiazolylene, tetrazolylene, thiadiazinylene, indolylene, isoindolylene, benzofurylene, benzothienylene, indazolylene, benzimidazolylene, benzthiazolylene, benzisothiazolylene, benzoxazolylene, benzisoxazolylene, purinylene, quinazolinylene, quinolizinylene, quinolinylene, isoquinolinylene, quinoxalinylene, naphthyridinylene, pteridinylene, carbazolylene, azepinylene, diazepinylene, acridinylene and

the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranylene, pyrrolinylene, pyrazolinylene, indolinylene, oxazolidinylene, oxazolinylene, oxazepinylene and the like.

The term "ArG1" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, and azulenyl as well as the corresponding divalent radicals.

The term "ArG2" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, fluorenyl, and indenyl, as well as the corresponding divalent radicals.

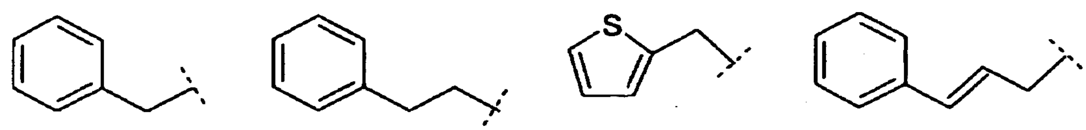
The term "Het1" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corresponding divalent radicals.

The term "Het2" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corresponding divalent radicals.

The term "Het3" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl,

1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thiooxothiazolidinyl, as well as the corresponding divalent radicals.

"Aryl-C_1-C_6-alkyl", "heteroaryl-C_1-C_6-alkyl", "aryl-C_2-C_6-alkenyl" etc. is intended to mean C_1-C_6-alkyl or C_2-C_6-alkenyl as defined above, substituted with an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

The term "substituted with one or more substituents" as used herein is intended to include one to four substituents, such as one to three substitients, one to two substituents, or even one substituent.

The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

When in the specification or claims mention is made of groups of compounds such as benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, these groups of compounds are intended to include also derivatives of the compounds from which the groups take their name.

The term "insulin" as used herein refers to human insulin as well as derivatives ans analogues hereof as defined below.

The term "human insulin" as used herein refers to insulin naturally produced in the human body or recombinantly produced insulin identical thereto. Recombinant human insulin may be produced in any suitable host cell, for example the host cells may be bacterial, fungal (including yeast), insect, animal or plant cells.

The term "insulin derivative" as used herein (and related terms) refers to human insulin or an analogue thereof in which at least one organic substituent is bound to one or more of the amino acids.

By the term "analogue of human insulin" as used herein (and related terms) is meant human insulin in which one or more amino acids have been deleted and/or replaced by other amino acids, including non-codeable amino acids, or human insulin comprising additional amino acids, i.e. more than 51 amino acids, such that the resulting analogue possesses insulin activity.

Rapid acting insulin is intended to mean human insulin, insulin analogues or insulin derivatives having an onset of action after injection or any other form of administration faster or equal to that of soluble and neutral formulations of human insulin.

The term "phenolic compound" or similar expressions as used herein refers to a compound in which a hydroxyl group is bound directly to a benzene or substituted benzene ring. Examples of such compounds include, but are not limited to, phenol, o-cresol, m-cresol, p-cresol, chloro-cresol, thymol, and 7-hydroxyindole.

DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that the two known ligand binding sites of the R-state insulin hexamer can be used to obtain an insulin preparation having improved physical and chemical stability.

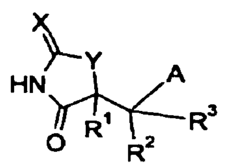
The basic concept underlying the present invention involves reversible attachment of a ligand to the His^{B10} Zn^{2+} site of the R-state hexamer. The anions currently used in insulin preparations as allosteric ligands for the R-state hexamers (notably chloride ion) bind only weakly to the His^{B10} anion site.

The His^{B10} Zn^{2+} site consists of a tunnel or cavity with a triangular-shaped cross-section that extends ~12 Å from the surface of the hexamer down to the His^{B10} Zn^{2+} ion. The diameter of the tunnel varies along its length and, depending on the nature of the ligand occupying the site, the opening can be capped over by the Asn^{B3} and Phe^{B1} side chains. The walls of the tunnel are made up of the side chains of the amino acid residues along one face each of the

three alpha-helices. The side chains from each helix that make up the lining of the tunnel are Phe^{B1}, Asn^{B3}, and Leu^{B6}. Therefore, except for the zinc ion, which is coordinated to three His^{B10} residues and is positioned at the bottom of the tunnel, the site is principally hydrophobic. Depending on the ligand structure, it may be possible for substituents on the ligand to make H-bonding interactions with Asn^{B3} and with the peptide linkage to Cys^{B7}.

In one aspect the invention provides a pharmaceutical composition comprising insulin and a zinc-binding ligand which reversibly binds to a His^{B10} Zn^{2+} site of an insulin hexamer, wherein the ligand is selected from the group consisting of benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In one embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



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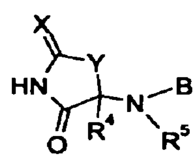


wherein

X is =O, =S or =NH

Y is -S-, -O- or -NH-

R^1 and R^4 are independently selected from hydrogen or C_1-C_6-alkyl,

R^2 is hydrogen or C_1-C_6-alkyl or aryl, R^1 and R^2 may optionally be combined to form a double bond,

R^3 and R^5 are independently selected from hydrogen, halogen, aryl, C_1-C_6-alkyl, or -C(O)$NR^{11}R^{12}$,

A and B are independently selected from C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^6 and the aryl or heteroaryl is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10},

A and R^3 may be connected through one or two valence bonds, B and R^5 may be connected through one or two valence bonds,

R^6 is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,
R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$NR^{11}S(O)_2R^{12}$, -$S(O)_2NR^{11}R^{12}$, -$S(O)NR^{11}R^{12}$, -$S(O)R^{11}$, -$S(O)_2R^{11}$, -$OS(O)_2$ R^{11}, -$C(O)NR^{11}R^{12}$, -$OC(O)NR^{11}R^{12}$, -$NR^{11}C(O)R^{12}$, -$CH_2C(O)NR^{11}R^{12}$, -OC_1-C_6-alkyl-$C(O)NR^{11}R^{12}$, -CH_2OR^{11}, -$CH_2OC(O)R^{11}$, -$CH_2NR^{11}R^{12}$, -$OC(O)R^{11}$, -OC_1-C_{15}-alkyl-$C(O)OR^{11}$, -OC_1-C_6-alkyl-OR^{11}, -SC_1-C_6-alkyl-$C(O)OR^{11}$, -C_2-C_6-alkenyl-$C(=O)OR^{11}$, -NR^{11}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{11}$, -NR^{11}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{11}$, -$C(O)OR^{11}$, $C(O)R^{11}$, or –C_2-C_6-alkenyl-$C(=O)R^{11}$, =O, or -C_2-C_6-alkenyl-C(=O)-$NR^{11}R^{12}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents independently selected from R^{13},

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, or C_3-C_8 cycloalkyl,

of which each cyclic moiety may optionally be substituted with one or more substituents independently selected from R^{14},

R^{11} and R^{12} are independently selected from hydrogen, OH, C_1-C_{20}-alkyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{13} is independently selected from halogen, -CN, -CF_3, -OCF_3, -OR^{11}, -$C(O)OR^{11}$, -$NR^{11}R^{12}$, and -$C(O)NR^{11}R^{12}$,

R^{14} is independently selected from halogen, $-C(O)OR^{11}$, $-CH_2C(O)OR^{11}$, $-CH_2OR^{11}$, -CN, -CF_3, $-OCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $S(O)_2R^{11}$, aryl and C_1-C_6-alkyl,

R^{15} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{16} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, -NO_2, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein X is =O or =S.

In another embodiment the invention provides a pharmaceutical composition wherein X is =O.

In another embodiment the invention provides a pharmaceutical composition wherein X is =S.

In another embodiment the invention provides a pharmaceutical composition wherein Y is -O- or -S-.

In another embodiment the invention provides a pharmaceutical composition wherein Y is -O-.

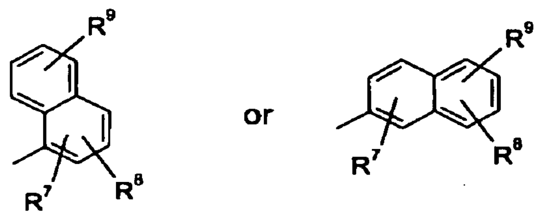
In another embodiment the invention provides a pharmaceutical composition wherein Y is -S-.

In another embodiment the invention provides a pharmaceutical composition wherein A is aryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is selected from ArG1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is phenyl or naphtyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



In another embodiment the invention provides a pharmaceutical composition wherein A is phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein A is heteroaryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is selected from Het1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

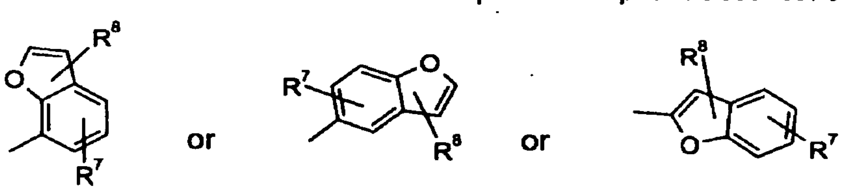
In another embodiment the invention provides a pharmaceutical composition wherein A is selected from Het2 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is selected from Het3 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thienyl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

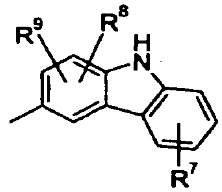
In another embodiment the invention provides a pharmaceutical composition wherein A is benzofuranyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



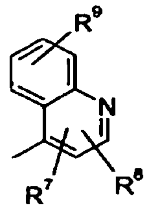
In another embodiment the invention provides a pharmaceutical composition wherein A is carbazolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is

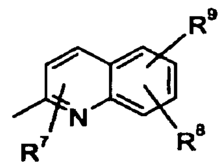


In another embodiment the invention provides a pharmaceutical composition wherein A is quinolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is

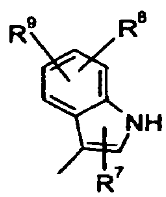


or

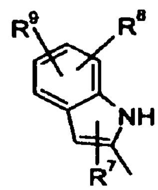


In another embodiment the invention provides a pharmaceutical composition wherein A is indolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



or



In another embodiment the invention provides a pharmaceutical composition wherein R^1 is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^2 is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^1 and R^2 are combined to form a double bond.

In another embodiment the invention provides a pharmaceutical composition wherein R^3 is C_1-C_6-alkyl, halogen, or $C(O)NR^{16}R^{17}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^3 is C_1-C_6-alkyl or $C(O)NR^{16}R^{17}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^3 is methyl.

In another embodiment the invention provides a pharmaceutical composition wherein B is phenyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein R^4 is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^5 is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^6 is aryl.

In another embodiment the invention provides a pharmaceutical composition wherein R^6 is phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-NR^{11}C(O)R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

In another embodiment the invention provides a pharmaceutical composition wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2\ R^{11}$, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

• C_1-C_6-alkyl or C_1-C_6-alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

In another embodiment the invention provides a pharmaceutical composition wherein R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2$ R^{11}, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

• C_1-C_6-alkyl or C_1-C_6- which may each optionally be substituted with one or more substituents independently selected from R^{13}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

In another embodiment the invention provides a pharmaceutical composition wherein R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

• C_1-C_6-alkyl which may each optionally be substituted with one or more substituents independently selected from R^{13} .

• aryl, aryloxy, aryl-C_1-C_6-alkoxy,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

In another embodiment the invention provides a pharmaceutical composition wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

- C_1-C_6-alkyl which may optionally be substituted with one or more substituents independently selected from R^{13}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds.

In another embodiment the invention provides a pharmaceutical composition wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{11} and R^{12} are independently selected from phenyl or phenyl-C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein one or both of R^{11} and R^{12} are methyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is independently selected from halogen, CF_3, OR^{11} or $NR^{11}R^{12}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is independently selected from halogen or OR^{11}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is OR^{11}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, -CN, -CF$_3$, -OR^{11}, S(O)$_2$R^{11}, and C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, or -OR^{11}.

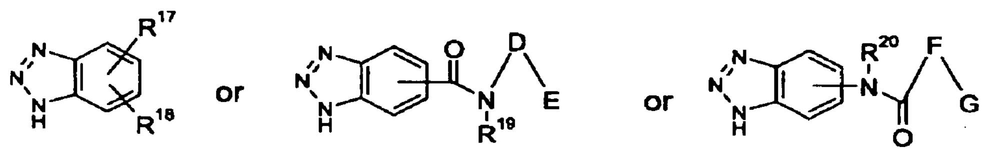
In another embodiment the invention provides a pharmaceutical composition wherein R^{15} is independently selected from halogen, -CN, -CF$_3$, -C(O)OC$_1$-C$_6$-alkyl,and –COOH.

In another embodiment the invention provides a pharmaceutical composition wherein R^{15} is independently selected from halogen or -C(O)OC$_1$-C$_6$-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{16} is independently selected from halogen, -C(O)OC$_1$-C$_6$-alkyl, -COOH, -NO$_2$, -OC$_1$-C$_6$-alkyl, -NH$_2$, C(=O) or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{16} is independently selected from halogen, -C(O)OC$_1$-C$_6$-alkyl, -COOH, -NO$_2$, or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



wherein

R^{19} is hydrogen or C_1-C_6-alkyl,

R^{20} is hydrogen or C_1-C_6-alkyl,

D and F are a valence bond or C_1-C_6-alkylene optionally substituted with one or more substituents independently selected from R^{72},

R^{72} is independently selected from hydroxy, C_1-C_6-alkyl, or aryl,

E is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23},

G is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26},

R^{17}, R^{18}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}S(O)_2R^{28}$, $-S(O)_2NR^{27}R^{28}$, $-S(O)NR^{27}R^{28}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$,or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents independently selected from R^{29},

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30},

R^{27} and R^{28} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{27} and R^{28} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{29} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{27}$, and $-NR^{27}R^{28}$,

R^{30} is independently selected from halogen, $-C(O)OR^{27}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$ and C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein D is a valence bond.

In another embodiment the invention provides a pharmaceutical composition wherein D is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

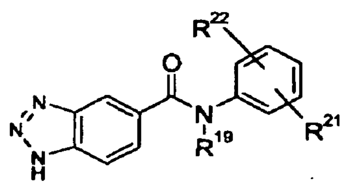
In another embodiment the invention provides a pharmaceutical composition wherein E is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

In another embodiment the invention provides a pharmaceutical composition wherein E is aryl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

In another embodiment the invention provides a pharmaceutical composition wherein E is selected from ArG1 and optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

In another embodiment the invention provides a pharmaceutical composition wherein E is phenyl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen; halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, -OCF_3, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -$NR^{27}C(O)R^{28}$, -$NR^{27}C(O)OR^{28}$, -$OC(O)R^{27}$, -OC_1-C_6-alkyl-$C(O)OR^{27}$, -SC_1-C_6-alkyl-$C(O)OR^{27}$, –C_2-C_6-alkenyl-$C(=O)OR^{27}$, -$C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, -C_1-C_6-alkyl-$C(=O)OR^{27}$, or -$C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, -OCF_3, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -$NR^{27}C(O)R^{28}$, -$NR^{27}C(O)OR^{28}$, -$OC(O)R^{27}$, -OC_1-C_6-alkyl-$C(O)OR^{27}$, -SC_1-C_6-alkyl-$C(O)OR^{27}$, –C_2-C_6-alkenyl-$C(=O)OR^{27}$, -$C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, -C_1-C_6-alkyl-$C(=O)OR^{27}$, or -$C(O)OR^{27}$,

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{19} is hydrogen or methyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{19} is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is Hydrogen, C_1-C_6-alkyl or aryl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{28} is hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein F is a valence bond.

In another embodiment the invention provides a pharmaceutical composition wherein F is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

In another embodiment the invention provides a pharmaceutical composition wherein G is C_1-C_6-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

In another embodiment the invention provides a pharmaceutical composition wherein G is C_1-C_6-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

In another embodiment the invention provides a pharmaceutical composition wherein G is C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein G is phenyl optionally substituted with up to three substituents R^{24}, R^{25}.and R^{26}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-

alkenyl-C(=O)OR^{27}-, -C(=O)NR^{27}-C_1-C_6-alkyl-C(=O)OR^{27}, -C_1-C_6-alkyl-C(=O)OR^{27}, or -C(O)OR^{27},

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{24}, R^{25} and R^{26} are independently selected from

• hydrogen, halogen, -OCF_3, -OR^{27}, -NR^{27}R^{28}, -SR^{27}, -NR^{27}C(O)R^{28}, -NR^{27}C(O)OR^{28}, -OC(O)R^{27}, -OC_1-C_6-alkyl-C(O)OR^{27}, -SC_1-C_6-alkyl-C(O)OR^{27}, –C_2-C_6-alkenyl-C(=O)OR^{27}, -C(=O)NR^{27}-C_1-C_6-alkyl-C(=O)OR^{27}, -C_1-C_6-alkyl-C(=O)OR^{27}, or -C(O)OR^{27},

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{24}, R^{25} and R^{26} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl
of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{20} is hydrogen or methyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{20} is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen, C_1-C_6-alkyl or aryl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen or C_1-C_6-alkyl or ArG1.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{28} is hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -S(O)R^{27}, -$S(O)_2R^{27}$, -C(O)$NR^{27}R^{28}$, -CH_2OR^{27}, -OC(O)R^{27}, -OC_1-C_6-alkyl-C(O)OR^{27}, -SC_1-C_6-alkyl-C(O)OR^{27}, or -C(O)OR^{27},

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, -CF_3, -NO_2, -OR^{27}, -$NR^{27}R^{28}$, or -C(O)OR^{27},

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}
- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{17} and R^{18} are independently selected from

- hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}
- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen or C_1-C_6-alkyl.

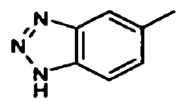
In another embodiment the invention provides a pharmaceutical composition wherein R^{27} is hydrogen, methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{28} is hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{28} is hydrogen, methyl or ethyl.

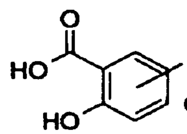
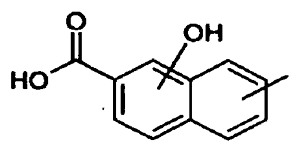
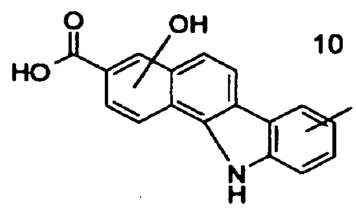
In another embodiment the invention provides a pharmaceutical composition wherein R^{72} is -OH or phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



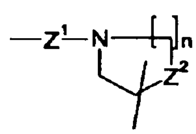
In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is of the form H-I-J

wherein H is

 or  or 

wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31}

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is -NH-, -O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{35}, -$C(O)R^{35}$, -$NR^{35}R^{36}$, -SR^{35}, -$NR^{35}S(O)_2R^{36}$, -$S(O)_2NR^{35}R^{36}$, -$S(O)NR^{35}R^{36}$, -$S(O)R^{35}$, -$S(O)_2R^{35}$, -$C(O)NR^{35}R^{36}$, -$OC(O)NR^{35}R^{36}$, -$NR^{35}C(O)R^{36}$, -$CH_2C(O)NR^{35}R^{36}$, -$OCH_2C(O)NR^{35}R^{36}$, -CH_2OR^{35}, -$CH_2NR^{35}R^{36}$, -$OC(O)R^{35}$, -OC_1-C_6-alkyl-$C(O)OR^{35}$, -SC_1-C_6-alkyl-$C(O)OR^{35}$ –C_2-C_6-alkenyl-$C(=O)OR^{35}$, -NR^{35}-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, -NR^{35}-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or -$C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

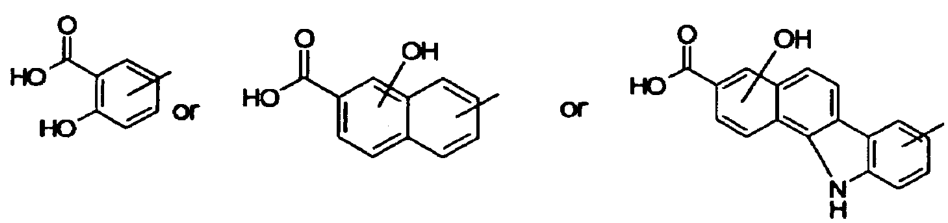
R^{34} is independently selected from halogen, -CN, -CF_3, -OCF_3, -OR^{35}, and -$NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{37} is independently selected from halogen, -$C(O)OR^{35}$, -C(O)H, -CN, -CF_3, -OCF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

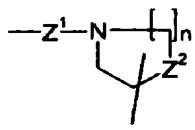
or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is of the form H-I-J, wherein H is



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31},

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is N,-O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

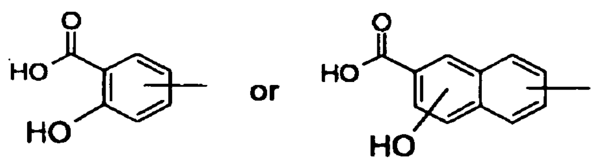
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

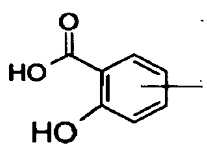
R^{37} is independently selected from halogen, -C(O)OR^{35}, -C(O)H, -CN, -CF$_3$, -OCF$_3$, -NO$_2$, -OR^{35}, -NR^{35}R^{36}, C$_1$-C$_6$-alkyl or C$_1$-C$_6$-alkanoyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base,
With the proviso that R^{31} and J cannot both be hydrogen.

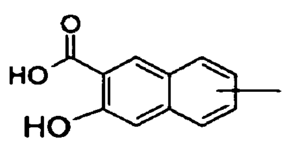
In another embodiment the invention provides a pharmaceutical composition wherein H is



In another embodiment the invention provides a pharmaceutical composition wherein H is



In another embodiment the invention provides a pharmaceutical composition wherein H is



In another embodiment the invention provides a pharmaceutical composition wherein I is a valence bond, –CH$_2$N(R^{32})-, or –SO$_2$N(R^{33})-.
In another embodiment the invention provides a pharmaceutical composition wherein I is a valence bond.
In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- C$_1$-C$_6$-alkyl, C$_2$-C$_6$-alkenyl or C$_2$-C$_6$-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF$_3$, -OCF$_3$, -OR^{35}, and -NR^{35}R^{36},
- aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- ArG1 or Het3, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37}.

In another embodiment the invention provides a pharmaceutical composition wherein J is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^{32} and R^{33} are independently selected from hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, -CN, -CF_3, -OCF_3, -SCF_3, -NO_2, -OR^{35}, -$C(O)R^{35}$, -$NR^{35}R^{36}$, -SR^{35}, -$C(O)NR^{35}R^{36}$, -$OC(O)NR^{35}R^{36}$, -$NR^{35}C(O)R^{36}$, -$OC(O)R^{35}$, -OC_1-C_6-alkyl-$C(O)OR^{35}$, -SC_1-C_6-alkyl-$C(O)OR^{35}$ or -$C(O)OR^{35}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, -CF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, -SR^{35}, -$NR^{35}C(O)R^{36}$, or -$C(O)OR^{35}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, -CF_3, -NO_2, -OR^{35}, -$NR^{35}R^{36}$, or -$NR^{35}C(O)R^{36}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, or -OR^{35}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl.

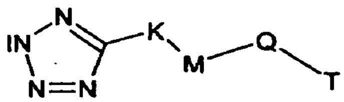
In another embodiment the invention provides a pharmaceutical composition wherein R^{35} and R^{36} are independently selected from hydrogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, -$C(O)OR^{35}$, -CN, -CF_3, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, -$C(O)OR^{35}$, -OR^{35}, -$NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, -$C(O)OR^{35}$ or -OR^{35}.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, -C_1-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -SR^{41}, -$NR^{41}S(O)_2R^{42}$, -$S(O)_2NR^{41}R^{42}$, -$S(O)NR^{41}R^{42}$, -$S(O)R^{41}$, -$S(O)_2R^{41}$, -$OS(O)_2$ R^{41}, -$C(O)NR^{41}R^{42}$, -$OC(O)NR^{41}R^{42}$, -$NR^{41}C(O)R^{42}$, -$CH_2C(O)NR^{41}R^{42}$, -OC_1-C_6-alkyl-$C(O)NR^{41}R^{42}$, -CH_2OR^{41}, -$CH_2OC(O)R^{41}$, -$CH_2NR^{41}R^{42}$, -$OC(O)R^{41}$, -OC_1-C_6-alkyl-$C(O)OR^{41}$, -OC_1-C_6-alkyl-OR^{41}, -S-C_1-C_6-alkyl-$C(O)OR^{41}$, -C_2-C_6-alkenyl-$C(=O)OR^{41}$, -NR^{41}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{41}$, -NR^{41}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{41}$, -$C(O)OR^{41}$, -C_2-C_6-alkenyl-$C(=O)R^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43},

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46}; R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{41}$, and $-NR^{41}R^{42}$

R^{44} is independently selected from halogen, $-C(O)OR^{41}$, $-CH_2C(O)OR^{41}$, $-CH_2OR^{41}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$ and C_1-C_6-alkyl,
R^{45} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl, -COOH and $-NH_2$,
R^{46} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, -OC_1-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and -COOH,

T is

- hydrogen,
- C_1-C_8-alkyl, C_2-C_8-alkenyl , C_2-C_8-alkynyl, C_1-C_8-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_8-alkyl, aroyl, aryl-C_1-C_8-alkoxy, aryl-C_2-C_8-alkenyl, aryl-C_2-C_8-alkyny-, heteroaryl, heteroaryl-C_1-C_8-alkyl, heteroaryl-C_2-C_8-alkenyl, heteroaryl-C_2-C_8-alkynyl,

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{50},

R^{50} is C_1-C_8-alkyl, C_1-C_8-alkoxy, aryl, aryloxy, aryl-C_1-C_8-alkoxy, -C(=O)-NH-C_1-C_8-alkyl-aryl, heteroaryl, heteroaryl-C_1-C_8-alkoxy, -C_1-C_8-alkyl-COOH, -O-C_1-C_8-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_8-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53},

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_8-alkyl,
R^{53} is independently selected from C_1-C_8-alkyl, C_1-C_8-alkoxy, -C_1-C_8-alkyl-COOH, -C_2-C_8-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{51}R^{52})$,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C_1-C_8-alkylene, -NH-C(=O)-U-, -C_1-C_8-alkyl-S-, -C_1-C_8-alkyl-O-, or -C(=O)-, wherein any C_1-C_8-alkyl moiety is optionally substituted with R^{38}.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C_1-C_8-alkylene, -NH-C(=O)-U-, -C_1-C_8-alkyl-S-, or -C_1-C_8-alkyl-O, wherein any C_1-C_8-alkyl moiety is optionally substituted with R^{38}.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C_1-C_8-alkylene, or -NH-C(=O)-U, wherein any C_1-C_8-alkyl moiety is optionally substituted with R^{38}.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond or C_1-C_8-alkylene, wherein any C_1-C_8-alkyl moiety is optionally substituted with R^{38}.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond or -NH-C(=O)-U.

In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond.

In another embodiment the invention provides a pharmaceutical composition wherein U is a valence bond or $-C_1-C_6$-alkyl-O-.

In another embodiment the invention provides a pharmaceutical composition wherein U is a valence bond.

In another embodiment the invention provides a pharmaceutical composition wherein M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

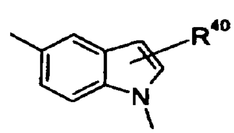
In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

In another embodiment the invention provides a pharmaceutical composition wherein M is phenylene optionally substituted with one or more substituents independently selected from R^{40}.

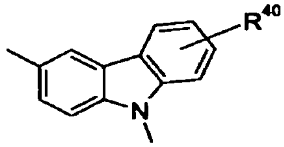
In another embodiment the invention provides a pharmaceutical composition wherein M is indolylene optionally substituted with one or more substituents independently selected from R^{40}.

In another embodiment the invention provides a pharmaceutical composition wherein M is



In another embodiment the invention provides a pharmaceutical composition wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R^{40}.

In another embodiment the invention provides a pharmaceutical composition wherein M is



In another embodiment the invention provides a pharmaceutical composition wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- aryl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, or heteroaryl-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1$-C_6-alkyl-$C(O)NR^{41}R^{42}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, ArG1-C_2-C_6-alkenyl, Het3, Het3-C_1-C_6-alkyl, or Het3-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{40} is selected from

- hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, =O, or $-NR^{41}C(O)R^{42}$,
- C_1-C_6-alkyl,
- ArG1.

In another embodiment the invention provides a pharmaceutical composition wherein R^{40} is selected from

- Halogen, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-C(O)OR^{41}$, or $-NR^{41}C(O)R^{42}$,
- Methyl,
- Phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{41} and R^{42} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

In another embodiment the invention provides a pharmaceutical composition wherein R^{41} and R^{42} are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

In another embodiment the invention provides a pharmaceutical composition wherein Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48}.

In another embodiment the invention provides a pharmaceutical composition wherein Q is a valence bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-CH_2-O-$, $-CH_2-NH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-$, $-NH-CH_2-CH_2-$, -NH-C(=O)-, -C(=O)-NH-, $-O-CH_2-$, $-O-CH_2-CH_2-$, or -C(=O)-.

In another embodiment the invention provides a pharmaceutical composition wherein R^{47} and R^{48} are independently selected from hydrogen, methyl and phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

In another embodiment the invention provides a pharmaceutical composition wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- ArG1, ArG1-C_1-C_6-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

In another embodiment the invention provides a pharmaceutical composition wherein T is

- hydrogen,

- C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from R^{50},
- phenyl, phenyl-C_1-C_6-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, heteroaryl, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -$S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -$N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy , -OR^{51}, -NO_2, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is C_1-C_6-alkyl, aryloxy, aryl-C_1-C_6-alkoxy, -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is C_1-C_6-alkyl, ArG1-O-, ArG1-C_1-C_6-alkoxy, -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

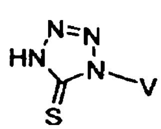
In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is phenyl, methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{50} is methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{51} is methyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{53} is C_1-C_6-alkyl, C_1-C_6-alkoxy, -OR^{51}, halogen,or -CF_3.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



wherein V is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55},

R^{54} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,
R^{55} is independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -SR^{56}, -$NR^{56}S(O)_2R^{57}$, -$S(O)_2NR^{56}R^{57}$, -$S(O)NR^{56}R^{57}$, -$S(O)R^{56}$, -$S(O)_2R^{56}$, -$OS(O)_2$ R^{56}, -$C(O)NR^{56}R^{57}$, -$OC(O)NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$, -$CH_2C(O)NR^{56}R^{57}$, -OC_1-C_6-alkyl-$C(O)NR^{56}R^{57}$, -CH_2OR^{56}, -$CH_2OC(O)R^{56}$, -$CH_2NR^{56}R^{57}$, -$OC(O)R^{56}$, -OC_1-C_6-alkyl-$C(O)OR^{56}$, -OC_1-C_6-alkyl-OR^{56}, -SC_1-C_6-alkyl-$C(O)OR^{56}$, –C_2-C_6-alkenyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{56}$, -$C(O)OR^{56}$, or –C_2-C_6-alkenyl-$C(=O)R^{56}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents selected from R^{58},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{59},

R^{56} and R^{57} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{60}, and the aryl groups may optionally be substituted with one or more substituents independently selected from R^{61}; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{58} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, $-OR^{56}$, and $-NR^{56}R^{57}$,

R^{59} is independently selected from halogen, $-C(O)OR^{56}$, $-CH_2C(O)OR^{56}$, $-CH_2OR^{56}$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{56}$, $-NR^{56}R^{57}$ and C_1-C_6-alkyl,

R^{60} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, $-C(=O)-R^{62}$, $-COOH$ and $-NH_2$,

R^{61} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, $-COOH$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OH$, $-OC_1$-C_6-alkyl, $-NH_2$, $C(=O)$ or C_1-C_6-alkyl,

R^{62} is C_1-C_6-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl independently,
or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein V is aryl, heteroaryl, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55}.
In another embodiment the invention provides a pharmaceutical composition wherein V is aryl, Het1, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.
In another embodiment the invention provides a pharmaceutical composition wherein V is aryl, Het2, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.
In another embodiment the invention provides a pharmaceutical composition wherein V is aryl, Het3, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

In another embodiment the invention provides a pharmaceutical composition wherein V is aryl optionally substituted with one or more substituents independently selected from R^{55}.

In another embodiment the invention provides a pharmaceutical composition wherein V is ArG1 optionally substituted with one or more substituents independently selected from R^{55}.

In another embodiment the invention provides a pharmaceutical composition wherein V is phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R^{55}.

In another embodiment the invention provides a pharmaceutical composition wherein V is phenyl optionally substituted with one or more substituents independently selected from R^{55}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_8-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, or heteroaryl-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_8-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- ArG1, ArG1-C_1-C_6-alkyl, Het3, or Het3-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$ or C_1-C_6-alkyl.

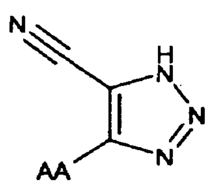
In another embodiment the invention provides a pharmaceutical composition wherein R^{55} is independently selected from halogen, -OR^{56}, -$NR^{56}R^{57}$, -$C(O)OR^{56}$, -OC_1-C_8-alkyl-$C(O)OR^{56}$, -$NR^{56}C(O)R^{57}$, methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{56} and R^{57} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, or -C(=O)-C_1-C_6-alkyl; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment the invention provides a pharmaceutical composition wherein R^{56} and R^{57} are independently selected from hydrogen or C_1-C_{12}-alkyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment the invention provides a pharmaceutical composition wherein R^{56} and R^{57} are independently selected from hydrogen or methyl, ethyl, propyl butyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment the invention provides a pharmaceutical composition 1 wherein the zinc-binding ligand is



wherein AA is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64},

R^{63} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,

R^{64} is independently selected from

• hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{65}, -$NR^{65}R^{66}$, -SR^{65}, -$NR^{65}S(O)_2R^{66}$, -$S(O)_2NR^{65}R^{66}$, -$S(O)NR^{65}R^{66}$, -$S(O)R^{65}$, -$S(O)_2R^{65}$, -$OS(O)_2$ R^{65}, -$C(O)NR^{65}R^{66}$, -$OC(O)NR^{65}R^{66}$, -$NR^{65}C(O)R^{66}$, -$CH_2C(O)NR^{65}R^{66}$, -OC_1-C_6-alkyl-$C(O)NR^{65}R^{66}$, -CH_2OR^{65}, -$CH_2OC(O)R^{65}$, -$CH_2NR^{65}R^{66}$, -$OC(O)R^{65}$, -OC_1-C_6-alkyl-$C(O)OR^{65}$, -OC_1-C_6-alkyl-OR^{65}, -SC_1-C_6-alkyl-$C(O)OR^{65}$, –C_2-C_6-alkenyl-

$C(=O)OR^{65}$, $-NR^{65}-C(=O)-C_1-C_6$-alkyl-$C(=O)OR^{65}$, $-NR^{65}-C(=O)-C_1-C_6$-alkenyl-$C(=O)OR^{65}$, $-C(O)OR^{65}$, or $-C_2-C_6$-alkenyl-$C(=O)R^{65}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents selected from R^{67},

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{68},

R^{65} and R^{66} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, $-C(=O)-R^{69}$, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted with one or more substituents selected from R^{70}, and the aryl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from R^{71}; R^{65} and R^{66} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{67} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{65}$, and $-NR^{65}R^{66}$,

R^{68} is independently selected from halogen, $-C(O)OR^{65}$, $-CH_2C(O)OR^{65}$, $-CH_2OR^{65}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$ and C_1-C_6-alkyl,

R^{69} is independently selected from C_1-C_6-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl,

R^{70} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1-C_6$-alkyl, $-C(O)OC_1-C_6$-alkyl, -COOH and $-NH_2$,

R^{71} is independently selected from halogen, $-C(O)OC_1-C_6$-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1-C_6$-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein AA is aryl, heteroaryl or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R^{64}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{64} is independently selected from hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, C_1-C_6-alkyl, $-OC(O)R^{65}$, $-OC_1$-C_6-alkyl-$C(O)OR^{65}$, aryl-C_2-C_6-alkenyl, aryloxy or aryl, wherein C_1-C_6-alkyl is optionally substituted with one or more substituents independently selected from R^{67}, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R^{68}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{64} is independently selected from halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, methyl, ethyl, propyl, $-OC(O)R^{65}$, $-OCH_2$-$C(O)OR^{65}$, $-OCH_2$-CH_2-$C(O)OR^{65}$, phenoxy optionally substituted with one or more substituents independently selected from R^{68}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently hydrogen, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R^{71} independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R^{71}.

In another embodiment the invention provides a pharmaceutical composition wherein R^{71} is halogen or C_1-C_6-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{71} is halogen or methyl.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is rapid acting insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is selected from the group consisting of human insulin, an analogue thereof, a derivative thereof, and combinations of any of these.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is an analogue of human insulin selected from the group consisting of

i. An analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; and

ii. des(B28-B30), des(B27) or des(B30) human insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is des(B30) human insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is is an analogue of human insulin wherein position B3 is Lys and position B29 is Glu or Asp.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin derivative is selected from the group consisting of B29-N^{ε}-myristoyl-des(B30) human insulin, B29-N^{ε}-palmitoyl-des(B30) human insulin, B29-N^{ε}-myristoyl human insulin, B29-N^{ε}-palmitoyl human insulin, B28-N^{ε}-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^{ε}-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^{ε}-myristoyl-$Thr^{B29}Lys^{B30}$ human insulin, B30-N^{ε}-palmitoyl-$Thr^{B29}Lys^{B30}$ human insulin, B29-N^{ε}-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^{ε}-(ω-carboxyheptadecanoyl) human insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin derivative is B29-N^{ε}-myristoyl-des(B30) human insulin.

In another embodiment the invention provides a pharmaceutical composition further comprising at least 3 molecules of a phenolic compound per insulin hexamer.

In another embodiment the invention provides a pharmaceutical composition further comprising an isotonicity agent.

In another embodiment the invention provides a pharmaceutical composition further comprising a buffer substance.

A method of stabilising an insulin preparation comprising adding a zinc-binding ligand to the insulin preparation.

A method of treating type 1 or type 2 diabetes comprising administering to a patient in need thereof a pharmaceutically effective dose of an insulin preparation.

In one embodiment of the invention the concentration of added ligand for the zinc site is between 0.2 and 10 times that of zinc ion in the preparation. In another embodiment the

concentration is between 0.5 and 5 times that of zinc ion. In another embodiment the ligand concentration is identical to that of zinc ion in the preparation.

The compounds of the present invention may be chiral, and it is intended that any enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system or more than one centre of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulphuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, picric, pyruvic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, , ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, *sec*-butyl-, *tert*-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as lysine, arginine and ornithine.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

In one embodiment of the invention the stabilized preparations are used in connection with insulin pumps. The insulin pumps may be prefilled and disposable, or the insulin preparations may be supplied from a reservoir which is removable. Insulin pumps may be skin-mounted or carried, and the path of the insulin preparation from the storage compartment of the pump to the patient may be more or less tortuous. The elevated temperature and increased physical stress the insulin preparation is thus exposed to challenges the stability of the constituent insulin. Non-limiting examples of insulin pumps are disclosed in US 5,957,895, US 5,858,001, US 4,468,221, US 4,468,221, US 5,957,895, US 5,858,001, US 6,074,369, US 5,858,001, US 5,527,288, and US 6,074,369.

In another embodiment the stabilized preparations are used in connection with pen-like injection devices, which may be prefilled and disposable, or the insulin preparations may be supplied from a reservoir which is removable. Non-limiting examples of pen-like injection devices are FlexPen®, InnoLet®, InDuo™, Innovo®.

In a further embodiment stabilized preparations are used in connection with devices for pulmonary administration of aqueous insulin preparations, a non-limiting example of which is the AerX® device.

In one aspect of the invention, the ligands are added to rapid acting insulin. The resulting preparations have improved physical and chemical stability while still retaining a high rate of absorbtion from subcutaneous tissue.

The present invention also relates to pharmaceutical compositions for the treatment of diabetes in a patient in need of such a treatment comprising an R-state hexamer of insulin according to the invention together with a pharmaceutically acceptable carrier.

In one embodiment of the invention the insulin preparation comprises 60 to 3000 nmol/ml of insulin.

In another embodiment of the invention the insulin preparation comprises 240 to 1200 nmol/ml of insulin.

In another embodiment of the invention the insulin preparation comprises about 600 nmol/ml of insulin.

Zinc ions may be present in an amount corresponding to 13 to 33 μg Zn/100 U insulin, more preferably 15 to 26 μg Zn/100 U insulin.

Insulin formulations of the invention are usually administered from multi-dose containers where a preservative effect is desired. Since phenolic preservatives also stabilize the R-state hexamer the formulations may contain up to 50 mM of phenolic molecules. Non-limiting examples of phenolic molecules are phenol, m-cresol, chloro-cresol, thymol, 7-hydroxyindole or any mixture thereof.

In one embodiment of the invention 0.5 to 4.0 mg/ml of phenolic compound may be employed.

In another embodiment of the invention 0.6 to 4.0 mg/ml of m-cresol may be employed.

In another embodiment of the invention 0.5 to 4.0 mg/ml of phenol may be employed.

In another embodiment of the invention 1.4 to 4.0 mg/ml of phenol may be employed.

In another embodiment of the invention 0.5 to 4.0 mg/ml of a mixture of m-cresol or phenol may be employed.

In another embodiment of the invention 1.4 to 4.0 mg/ml of a mixture of m-cresol or phenol may be employed.

The pharmaceutical preparation may further comprise a buffer substance, such as a TRIS, phosphate, glycine or glycylglycine (or another zwitterionic substance) buffer, an isotonicity agent, such as NaCl, glycerol, mannitol and/or lactose. Chloride would be used at moderate concentrations, in one embodiment of the invention up to 50 mM to avoid competition with the zinc-site ligands of the present invention. In another embodiment the chloride concentration would be from 3 to 20 mM.

The *in vivo* action of insulin may be modified by the addition of physiologically acceptable agents that increase the viscosity of the pharmaceutical preparation. Thus, the pharmaceutical preparation according to the invention may furthermore comprise an agent which increases the viscosity, such as polyethylene glycol, polypropylene glycol, copolymers thereof, dextrans and/or polylactides.

In one embodiment the insulin preparation of the invention comprises between 0.0005 % by weight and 1 % by weight of a non-ionic or zwitter-ionic surfactant, for example tween 20 or

Polox 188. A nonionic detergent can be added to stabilise insulin against fibrillation during storage and handling.
The insulin preparation of the present invention may have a pH value in the range of 3.0 to 8.5, e.g. 7.4 to 7.9.

EXAMPLES

The following examples and general procedures refer to intermediate compounds and final products identified in the specification and in the synthesis schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of compounds of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

HPLC-MS (Method A)

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis was performed at 40 °C by injecting an appropriate volume of the sample (preferably 1 μL) onto the column, which was eluted with a gradient of acetonitrile. The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile lineary during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

HPLC-MS (Method B)

The following instrumentation was used:

Sciex API 100 Single quadropole mass spectrometer

Perkin Elmer Series 200 Quard pump

Perkin Elmer Series 200 autosampler

Applied Biosystems 785A UV detector

Sedex 55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

A: Acetonitrile

B: Water

C: 0.5% TFA in water

D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

The analysis was perfomed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

The remaining 1.48 mL/min was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	YMC ODS-A 120Å s - 5µ 3 mm x 50 mm id	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min	
Detection	UV: 214 nm	ELS: 40 °C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

HPLC-MS (Method C) The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G1315A DAD diode array detector

- Hewlett Packard series 1100 MSD
- Sedere 75 Evaporative Light Scattering detector

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A	0.01% TFA in water
B	0.01% TFA in acetonitrile

The analysis is performed at 40 °C by injecting an appropriate volume of the sample (preferably 1 μl) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id 5 μm
Gradient	5% - 100% acetonitrile linear during 7.5 min at 1.5 ml/min
Detection	210 nm (analogue output from DAD) ELS (analogue output from ELS)
MS	ionisation mode API-ES Scan 100-1000 amu step 0.1 amu

After the DAD the flow is divided yielding approximately 1 ml/min to the ELS and 0.5 ml/min to the MS.

HPLC-MS (Method D)

The following instrumentation was used:

Sciex API 150 Single Quadropole mass spectrometer

Hewlett Packard Series 1100 G1312A Bin pump

Gilson 215 micro injector

Hewlett Packard Series 1100 G1315A DAD diode array detector

Sedex 55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh Power G3 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

A: Acetonitrile containing 0.05% TFA

B: Water containing 0.05% TFA

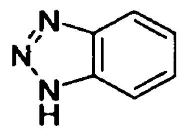
The requirements for the samples are that they contain approximately 500 µg/ml of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)
The analysis was performed at room temperature by injecting 20 µl of the sample solution on the column, which was eluted with a gradient of acetonitrile in 0.05% TFA
The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µl/min through approx. 1 m 75 µ fused silica capillary to the API interface of API 150 spectrometer.
The remaining 1.48 ml/min was passed through the UV detector and to the ELS detector.
During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.
The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	Waters X-terra C18 5µ 3 mm x 50 mm id			
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 ml/min			
Detection	UV: 214 nm		ELS: 40 °C	
MS	Experiment: Dwell: Method:	Start: 100 amu 0.571 msec Scan 284 times = 9.5 min	Stop: 800 amu	Step: 0.2 amu

EXAMPLES

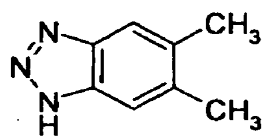
Example 1

1*H*-Benzotriazole



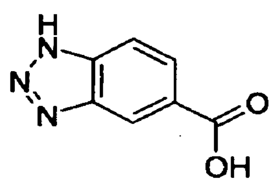
Example 2

5,6-Dimethyl-1*H*-benzotriazole



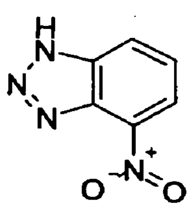
Example 3

1*H*-Benzotriazole-5-carboxylic acid



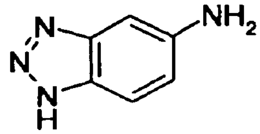
Example 4

4-Nitro-1*H*-benzotriazole



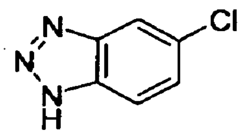
Example 5

5-Amino-1*H*-benzotriazole



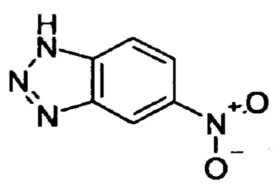
Example 6

5-Chloro-1*H*-benzotriazole



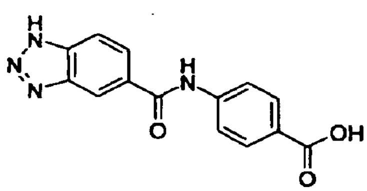
Example 7

5-Nitro-1*H*-benzotriazole



Example 8

4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid

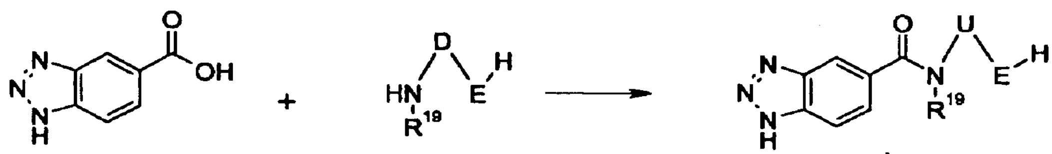


4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester (5.2 g, 17.6 mmol) was dissolved in THF (60 mL) and methanol (10 mL) was added followed by 1N sodium hydroxide (35 mL). The mixture was stirred at room temperature for 16 hours and then 1N hydrochloric acid (45 mL) was added. The mixture was added water (200 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic phases were evaporated *in vacuo* to afford 0.44 g of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid. By filtration of the

aqueous phase a further crop of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid was isolated (0.52 g).

^{1}H-NMR (DMSO-d_6): δ 7.97 (4H, s), 8.03 (2H, m), 8.66 (1H, bs), 10.7 (1H, s), 12.6 (1H, bs); HPLC-MS (Method A): m/z: 283 (M+1); Rt = 1.85 min.

General procedure (A) for preparation of compounds of general formula I_1:



I_1

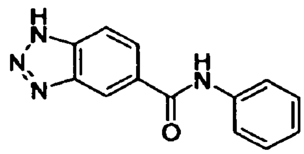
wherein D, E and R^{19} are as defined above, and E is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23} independently as defined above.

The carboxylic acid of 1H-benzotriazole-5-carboxylic acid is activated, ie the OH functionality is converted into a leaving group L (selected from eg fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyloxy, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinyloxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy, benzotriazole 5-COO, or any other leaving group known to act as a leaving group in acylation reactions. The activated benzotriazole-5-carboxylic acid is then reacted with R^2-$(CH_2)_n$-B' in the presence of a base. The base can be either absent (i.e. R^2-$(CH_2)_n$-B' acts as a base) or triethylamine, N-ethyl-N,N.-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in acylation reactions. The reaction is performed in a solvent solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reaction is performed between 0 °C and 80 °C, preferably between 20 °C and 40 °C. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (A) is further illustrated in the following example:

Example 9 (General Procedure (A))

1*H*-Benzotriazole-5-carboxylic acid phenylamide



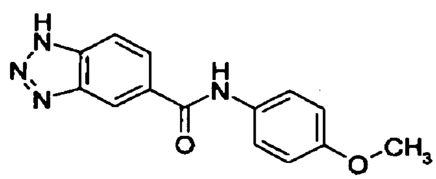
Benzotriazole-5-carboxylic acid (856 mg), HOAt (715 mg) and EDAC (1.00 g) were dissolved in DMF (17.5 mL) and the mixture was stirred at room temperature 1 hour. A 0.5 mL aliqot of this mixture was added to aniline (13.7 μL, 0.15 mmol) and the resulting mixture was vigorously shaken at room temperature for 16 hours. 1N hydrochloric acid (2 mL) and ethyl acetate (1 mL) were added and the mixture was vigorously shaken at room temperature for 2 hours. The organic phase was isolated and concentrated *in vacuo* to afford the title compound.

HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

The compounds in the following examples were similarly made. Optionally, the compounds may be isolated by filtration or by chromatography.

Example 10 (General Procedure (A))

1*H*-Benzotriazole-5-carboxylic acid (4-methoxyphenyl)amide

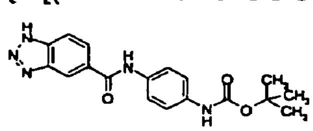


HPLC-MS (Method A): m/z: 269 (M+1) & 291 (M+23); Rt = 2.41 min

HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

Example 11 (General Procedure (A))

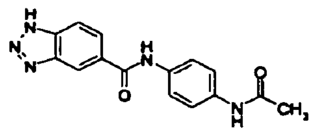
{4-[(1*H*-Benzotriazole-5-carbonyl)amino]phenyl}carbamic acid *tert*-butyl ester



HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.58 min.

Example 12 (General Procedure (A))

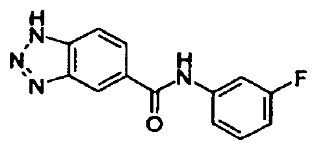
1*H*-Benzotriazole-5-carboxylic acid (4-acetylaminophenyl)amide



HPLC-MS (Method B): m/z: 296 (M+1); Rt = 3.32 min.

Example 13 (General Procedure (A))

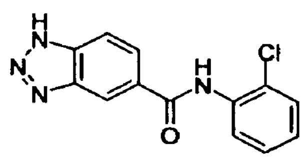
1*H*-Benzotriazole-5-carboxylic acid (3-fluorophenyl)amide



HPLC-MS (Method B): m/z: 257 (M+1); Rt = 4.33 min.

Example 14 (General Procedure (A))

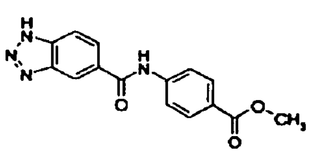
1*H*-Benzotriazole-5-carboxylic acid (2-chlorophenyl)amide



HPLC-MS (Method B): m/z: 273 (M+1); Rt = 4.18 min.

Example 15 (General Procedure (A))

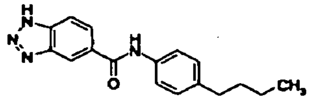
4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester



HPLC-MS (Method A):m/z: 297 (M+1); Rt : 2,60 min. HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.30 min.

Example 16 (General Procedure (A))

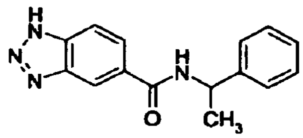
1*H*-Benzotriazole-5-carboxylic acid (4-butylphenyl)amide



HPLC-MS (Method B): m/z: 295 (M+1); Rt = 5.80 min.

Example 17 (General Procedure (A))

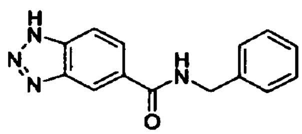
1*H*-Benzotriazole-5-carboxylic acid (1-phenylethyl)amide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

Example 18 (General Procedure (A))

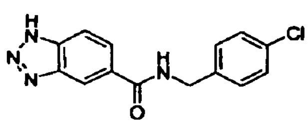
1*H*-Benzotriazole-5-carboxylic acid benzylamide



HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.88 min.

Example 19 (General Procedure (A))

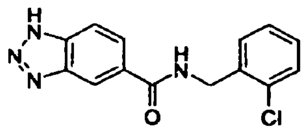
1*H*-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide



HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

Example 20 (General Procedure (A))

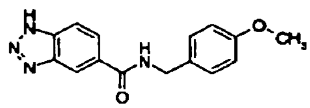
1*H*-Benzotriazole-5-carboxylic acid 2-chlorobenzylamide



HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.25 min.

Example 21 (General Procedure (A))

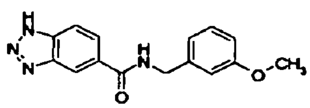
1*H*-Benzotriazole-5-carboxylic acid 4-methoxybenzylamide



HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.93 min.

Example 22 (General Procedure (A))

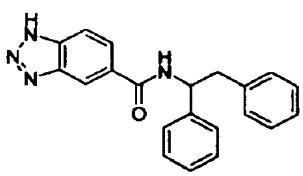
1*H*-Benzotriazole-5-carboxylic acid 3-methoxybenzylamide



HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.97 min.

Example 23 (General Procedure (A))

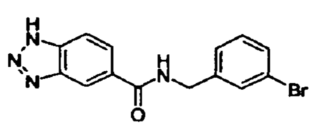
1*H*-Benzotriazole-5-carboxylic acid (1,2-diphenylethyl)amide



HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.05 min.

Example 24 (General Procedure (A))

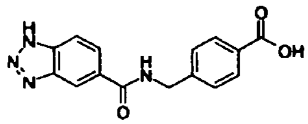
1*H*-Benzotriazole-5-carboxylic acid 3-bromobenzylamide



HPLC-MS (Method B): m/z: 331 (M+1); Rt = 4.45 min.

Example 25 (General Procedure (A))

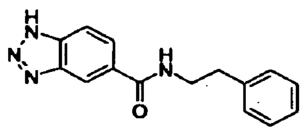
4-{[(1*H*-Benzotriazole-5-carbonyl)amino]methyl}benzoic acid



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.35 min.

Example 26 (General Procedure (A))

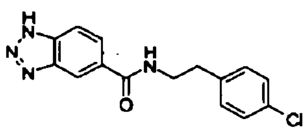
1*H*-Benzotriazole-5-carboxylic acid phenethylamide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

Example 27 (General Procedure (A))

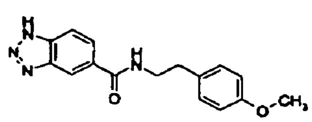
1*H*-Benzotriazole-5-carboxylic acid [2-(4-chlorophenyl)ethyl]amide



HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.50 min.

Example 28 (General Procedure (A))

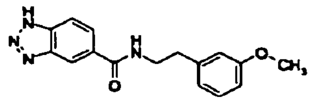
1*H*-Benzotriazole-5-carboxylic acid [2-(4-methoxyphenyl)ethyl]amide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.15 min.

Example 29 (General Procedure (A))

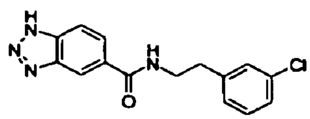
1*H*-Benzotriazole-5-carboxylic acid [2-(3-methoxyphenyl)ethyl]amide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.13 min.

Example 30 (General Procedure (A))

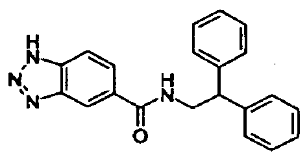
1*H*-Benzotriazole-5-carboxylic acid [2-(3-chlorophenyl)ethyl]amide



HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.55 min.

Example 31 (General Procedure (A))

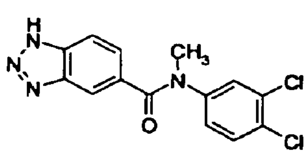
1*H*-Benzotriazole-5-carboxylic acid (2,2-diphenylethyl)amide



HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.00 min.

Example 32 (General Procedure (A))

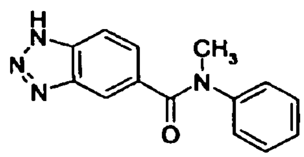
1*H*-Benzotriazole-5-carboxylic acid (3,4-dichlorophenyl)methylamide



HPLC-MS (Method B): m/z: 321 (M+1); Rt = 4.67 min.

Example 33 (General Procedure (A))

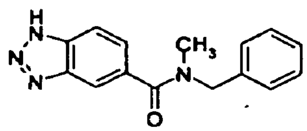
1*H*-Benzotriazole-5-carboxylic acid methylphenylamide



HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.82 min.

Example 34 (General Procedure (A))

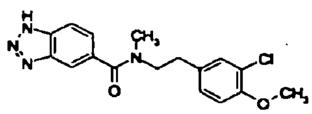
1*H*-Benzotriazole-5-carboxylic acid benzylmethylamide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.05 min.

Example 35 (General Procedure (A))

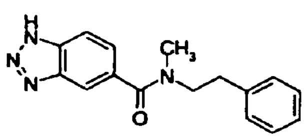
1*H*-Benzotriazole-5-carboxylic acid [2-(3-chloro-4-methoxyphenyl)ethyl]methyl-amide



HPLC-MS (Method B): m/z: 345 (M+1); Rt = 4.37 min.

Example 36 (General Procedure (A))

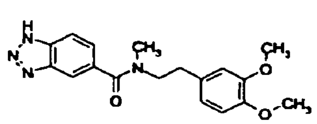
1*H*-Benzotriazole-5-carboxylic acid methylphenethylamide



HPLC-MS (Method B): m/z: 281 (M+1); Rt = 4.15 min.

Example 37 (General Procedure (A))

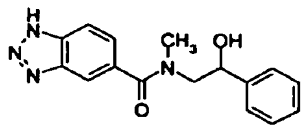
1*H*-Benzotriazole-5-carboxylic acid [2-(3,4-dimethoxyphenyl)ethyl]methylamide



HPLC-MS (Method B): m/z: 341 (M+1); Rt = 3.78 min;

Example 38 (General Procedure (A))

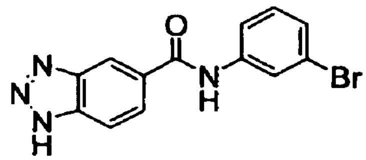
1*H*-Benzotriazole-5-carboxylic acid (2-hydroxy-2-phenylethyl)methylamide



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.48 min.

Example 39 ***(General procedure (A))***

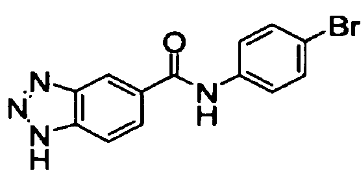
1H-Benzotriazole-5-carboxylic acid (3-bromophenyl)amide



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.19 min.

Example 40 ***(General procedure (A))***

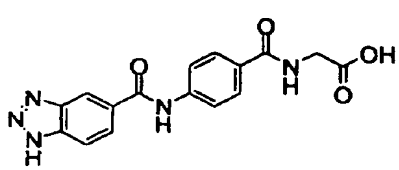
1H-Benzotriazole-5-carboxylic acid (4-bromophenyl)amide



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.18 min.

Example 41 ***(General procedure (A))***

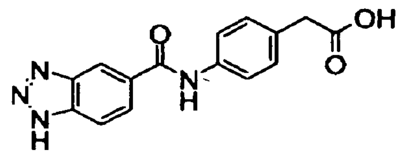
{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}acetic acid



HPLC-MS (Method A): m/z: 340 (M+1); Rt = 1.71 min.

Example 42 ***(General procedure (A))***

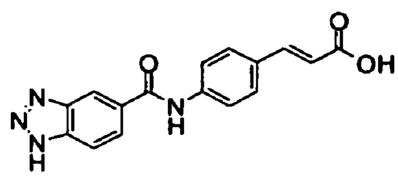
{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.02 min.

Example 43 ***(General procedure (A))***

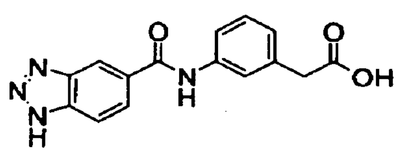
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acrylic acid



HPLC-MS (Method A): m/z: 309 (M+1); Rt = 3.19 min.

Example 44 ***(General procedure (A))***

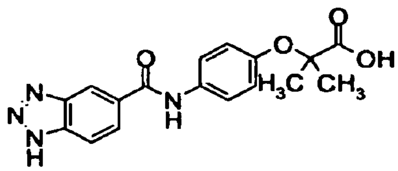
{3-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.10 min.

Example 45 ***(General procedure (A))***

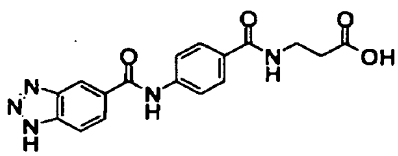
2-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenoxy}-2-methylpropionic acid



HPLC-MS (Method A): m/z: 341 (M+1); Rt = 2.42 min.

Example 46 ***(General procedure (A))***

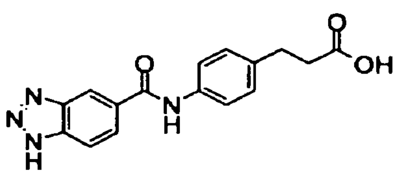
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}propionic acid



HPLC-MS (Method A): m/z: 354 (M+1); Rt = 1.78 min.

Example 47 ***(General procedure (A))***

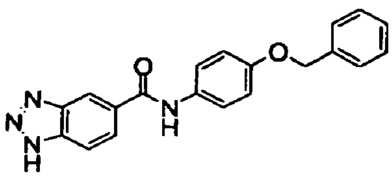
3-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}propionic acid



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 2.20 min.

Example 48 ***(General procedure (A))***

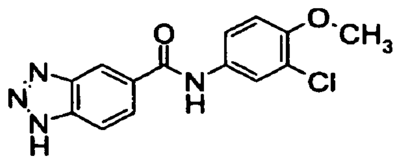
1H-Benzotriazole-5-carboxylic acid (4-benzyloxyphenyl)amide



HPLC-MS (Method A): m/z: 345 (M+1); Rt = 3.60 min.

Example 49 ***(General procedure (A))***

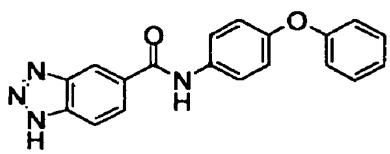
1H-Benzotriazole-5-carboxylic acid (3-chloro-4-methoxyphenyl)amide



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.88 min.

Example 50 ***(General procedure (A))***

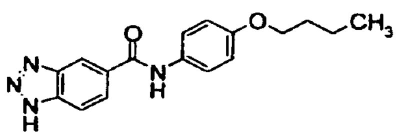
1H-Benzotriazole-5-carboxylic acid (4-phenoxyphenyl)amide



HPLC-MS (Method A): m/z: 331 (M+1); Rt = 3.62 min.

Example 51 ***(General procedure (A))***

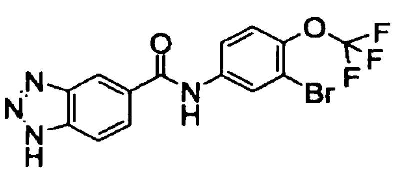
1H-Benzotriazole-5-carboxylic acid (4-butoxyphenyl)amide



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 3.59 min.

Example 52 ***(General procedure (A))***

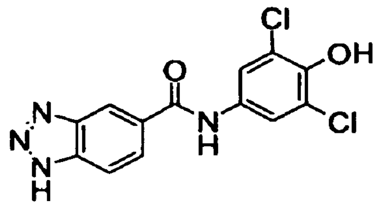
1H-Benzotriazole-5-carboxylic acid (3-bromo-4-trifluoromethoxyphenyl)amide



HPLC-MS (Method A): m/z: 402 (M+1); Rt = 3.93 min.

Example 53 ***(General procedure (A))***

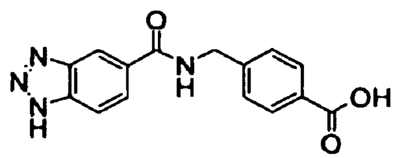
1H-Benzotriazole-5-carboxylic acid (3,5-dichloro-4-hydroxyphenyl)amide



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 2.57 min.

Example 54 ***(General procedure (A))***

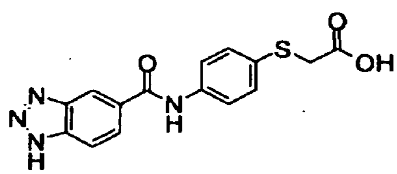
4-{[(1H-Benzotriazole-5-carbonyl)amino]methyl}benzoic acid



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 1.86 min.

Example 55 ***(General procedure (A))***

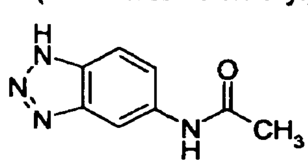
{4-[(1H-Benzotriazole-5-carbonyl)amino]phenylsulfanyl}acetic acid



HPLC-MS (Method A): m/z: 329 (M+1); Rt = 2.34 min.

Example 56

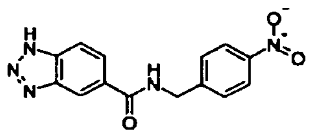
N-(1*H*-Benzotriazol-5-yl)acetamide



HPLC-MS (Method A): m/z: 177 (M+1); Rt = 0.84 min.

Example 57 (General Procedure (A))

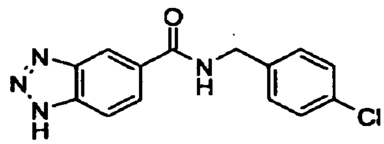
1*H*-Benzotriazole-5-carboxylic acid 4-nitrobenzylamide



The following compound is prepared according to general procedure (N) as described below:

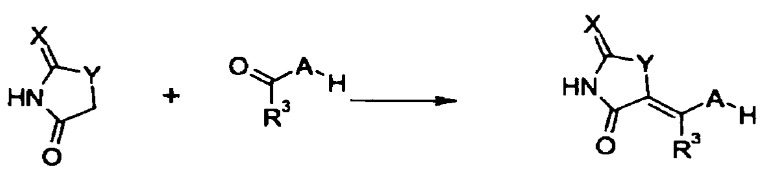
Example 58 **(General procedure (N))**

1*H*-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide



HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

General procedure (B) for preparation of compounds of general formula I_2:



I_2

wherein X, Y, A and R^3 are as defined above and A is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} as defined above.

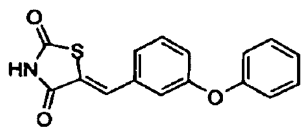
The chemistry is well known (eg Lohray et al., *J. Med. Chem.*, **1999**, *42*, 2569-81) and is generally performed by reacting a carbonyl compound (aldehyde or ketone) with the heterocyclic ring (eg thiazolidine-2,4-dione (X = O; Y = S), rhodanine (X = Y = S) and hydantoin (X = O; Y = NH) in the presence of a base, such as sodium acetate, potassium acetate, ammonium acetate, piperidinium benzoate or an amine (eg piperidine, triethylamine and the like) in a solvent (eg acetic acid, ethanol, methanol, DMSO, DMF, NMP, toluene, benzene) or in a mixture of two or more of these solvents. The reaction is performed at room

temperature or at elevated temperature, most often at or near the boiling point of the mixture. Optionally, azeotropic removal of the formed water can be done.

This general procedure (B) is further illustrated in the following example:

Example 59 (General procedure (B))

5-(3-Phenoxybenzylidene)thiazolidine-2,4-dione



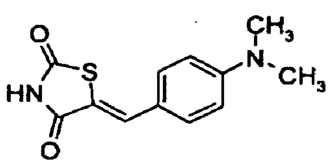
A solution of thiazolidine-2,4-dione (90%, 78 mg, 0.6 mmol) and ammonium acetate (92 mg, 1.2 mmol) in acetic acid (1 mL) was added to 3-phenoxybenzaldehyde (52 μL, 0.6 mmol) and the resulting mixture was shaken at 115 °C for 16 hours. After cooling, the mixture was concentrated *in vacuo* to afford the title compound.

HPLC-MS (Method A): m/z: 298 (M+1); Rt = 4.54 min.

The compounds in the following examples were similarly prepared. Optionally, the compounds can be further purified by filtration and washing with water, ethanol and / or heptane instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by chromatography, such as preparative HPLC.

Example 60 (General procedure (B))

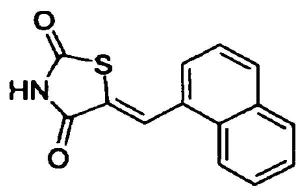
5-(4-Dimethylaminobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 249 (M+1); Rt = 4.90 min

Example 61 (General procedure (B))

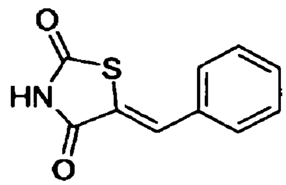
5-Naphthalen-1-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4,16 min.

Example 62 (General procedure (B))

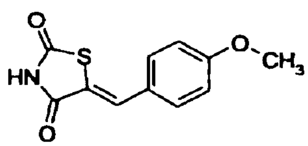
5-Benzylidene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 206 (M+1); Rt = 4,87 min.

Example 63 (General procedure (B))

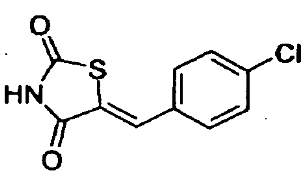
5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 263 (M+1); Rt = 4,90 min.

Example 64 (General procedure (B))

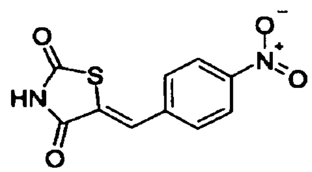
5-(4-Chloro-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 5,53 min.

Example 65 (General procedure (B))

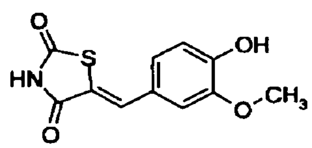
5-(4-Nitro-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 251 (M+1); Rt = 4,87 min.

Example 66 (General procedure (B))

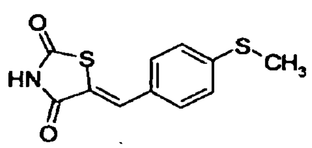
5-(4-Hydroxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 252 (M+1); Rt = 4,07 min.

Example 67 (General procedure (B))

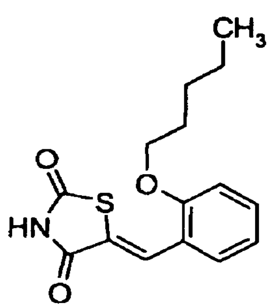
5-(4-Methylsulfanylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 252 (M+1); Rt = 5,43 min.

Example 68 (General procedure (B))

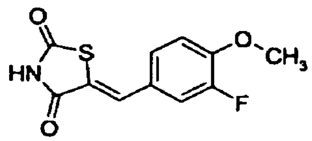
5-(2-Pentyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 292 (M+1); Rt = 4.75 min.
^{1}H NMR (DMSO-d_6): δ = 0.90 (3H, t), 1.39 (4H, m), 1.77 (2H, p), 4.08 (2H, t), 7.08 (1H, t), 7.14 (1H, d), 7.43 (2H, m), 8.03 (1H, s), 12.6 (1H, bs).

Example 69 (General procedure (B))

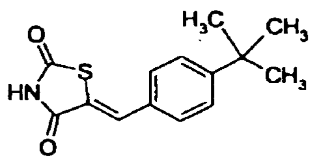
5-(3-Fluoro-4-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 354 (M+1); Rt = 4,97 min.

Example 70 (General procedure (B))

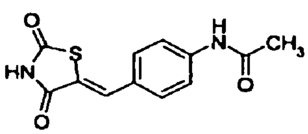
5-(4-tert-Butylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 262 (M+1); Rt = 6,70 min.

Example 71 (General procedure (B))

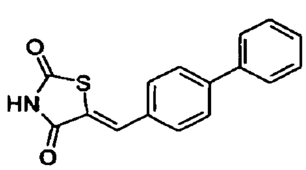
N-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acetamide



HPLC-MS (Method A): m/z: 263 (M+1); Rt = 3,90 min.

Example 72 (General procedure (B))

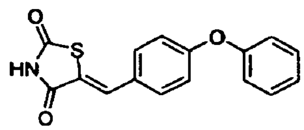
5-Biphenyl-4-ylmethylene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 282 (M+1); Rt = 4,52 min.

Example 73 (General procedure (B))

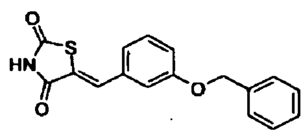
5-(4-Phenoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 298 (M+1); Rt = 6,50 min.

Example 74 (General procedure (B))

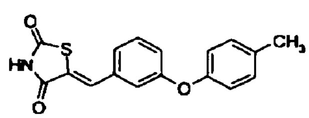
5-(3-Benzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,37 min.

Example 75 (General procedure (B))

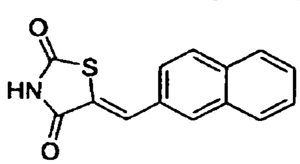
5-(3-p-Tolyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,87 min.

Example 76 (General procedure (B))

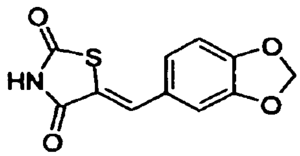
5-Naphthalen-2-ylmethylene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4.15 min.

Example 77 (General procedure (B))

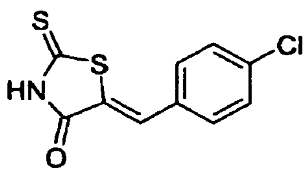
5-Benzo[1,3]dioxol-5-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1), Rt = 3.18 min.

Example 78 (General procedure (B))

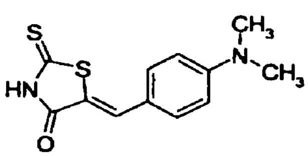
5-(4-Chlorobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4,51 min.

Example 79 (General procedure (B))

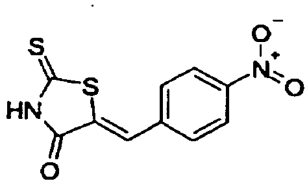
5-(4-Dimethylaminobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 265 (M+1); Rt = 5,66 min.

Example 80 (General procedure (B))

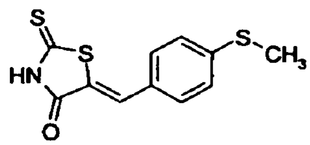
5-(4-Nitrobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3,94 min.

Example 81 (General procedure (B))

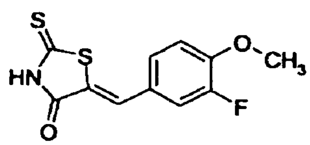
5-(4-Methylsulfanylbenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 268 (M+1); Rt = 6,39 min.

Example 82 (General procedure (B))

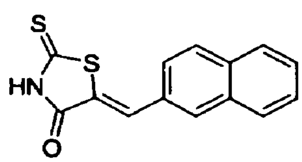
5-(3-Fluoro-4-methoxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 5,52 min.

Example 83 (General procedure (B))

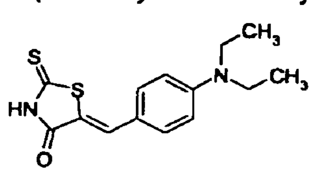
5-Naphthalen-2-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,75 min.

Example 84 (General procedure (B))

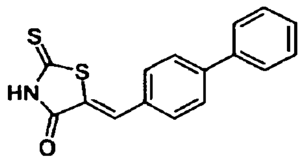
5-(4-Diethylaminobenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 293 (M+1); Rt = 5,99 min.

Example 85 (General procedure (B))

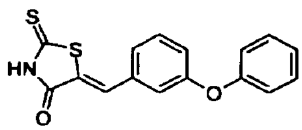
5-Biphenyl-4-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 298 (M+1); Rt = 7,03 min.

Example 86 (General procedure (B))

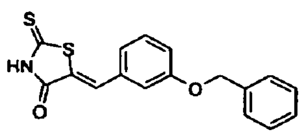
5-(3-Phenoxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 314 (M+1); Rt = 6,89 min.

Example 87 (General procedure (B))

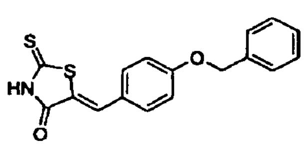
5-(3-Benzyloxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 328 (M+1); Rt = 6,95 min.

Example 88 (General procedure (B))

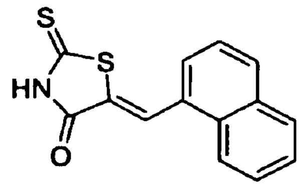
5-(4-Benzyloxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 328 (M+1); RT = 6,89 min.

Example 89 (General procedure (B))

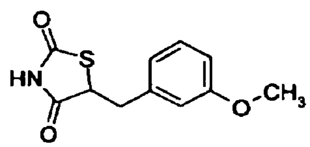
5-Naphthalen-1-ylmethylene-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,43 min.

Example 90 (General procedure (B))

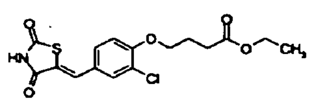
5-(3-Methoxybenzyl)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 236 (M+1); Rt = 3,05 min.

Example 91 (General procedure (D))

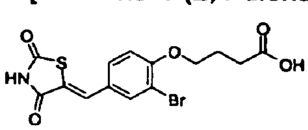
4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid ethyl ester



HPLC-MS (Method A): m/z: 392 (M+23), Rt = 4.32 min.

Example 92 (General procedure (D))

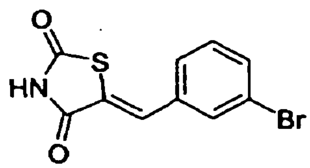
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenoxy]-butyric acid



HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3,35 min.

Example 93 (General procedure (B))

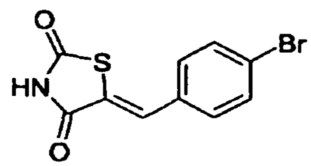
5-(3-Bromobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.01 min.

Example 94 (General procedure (B))

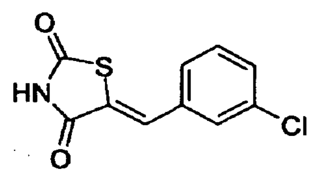
5-(4-Bromobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.05 min.

Example 95 (General procedure (B))

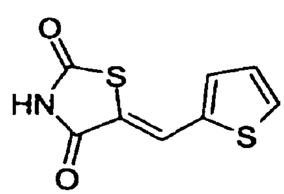
5-(3-Chlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 3.91 min.

Example 96 (General procedure (B))

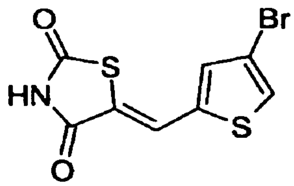
5-Thiophen-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 212 (M+1); Rt = 3.09 min.

Example 97 (General procedure (B))

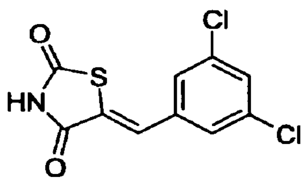
5-(4-Bromothiophen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 291 (M+1); Rt = 3.85 min.

Example 98 (General procedure (B))

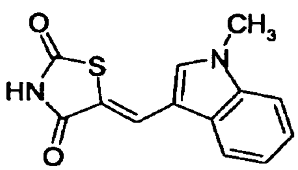
5-(3,5-Dichlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 274 (M+1); Rt = 4.52 min.

Example 99 (General procedure (B))

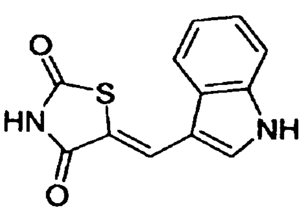
5-(1-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.55 min.

Example 100 (General procedure (B))

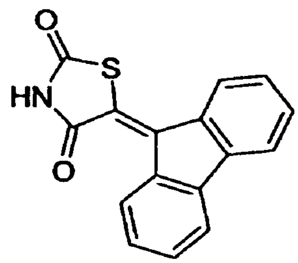
5-(1H-Indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 245 (M+1); Rt = 2.73 min.

Example 101 (General procedure (B))

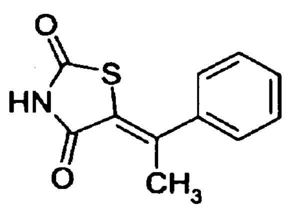
5-Fluoren-9-ylidenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 280 (M+1); Rt = 4.34 min.

Example 102 (General procedure (B))

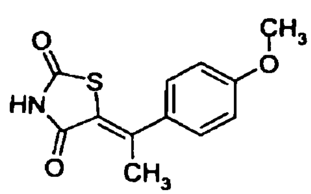
5-(1-Phenylethylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 220 (M+1); Rt = 3,38 min.

Example 103 (General procedure (B))

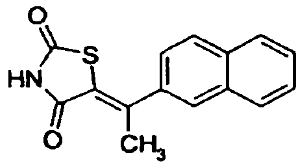
5-[1-(4-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3.55 min.

Example 104 (General procedure (B))

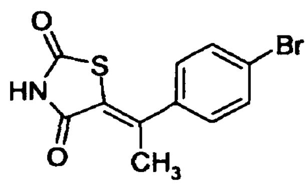
5-(1-Naphthalen-2-yl-ethylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,30 min.

Example 105 (General procedure (B))

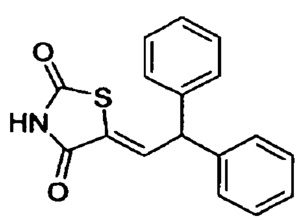
5-[1-(4-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,18 min.

Example 106 (General procedure (B))

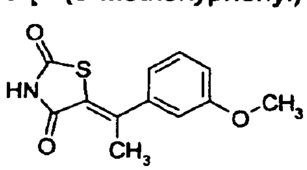
5-(2,2-Diphenylethylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 296 (M+1); Rt = 4,49 min.

Example 107 (General procedure (B))

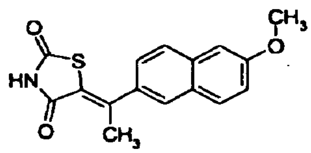
5-[1-(3-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3,60 min.

Example 108 (General procedure (B))

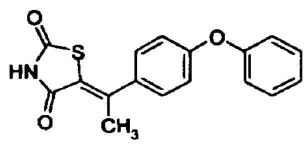
5-[1-(6-Methoxynaphthalen-2-yl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,26 min.

Example 109 (General procedure (B))

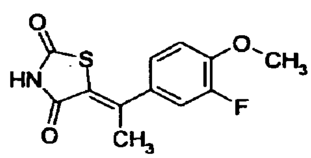
5-[1-(4-Phenoxyphenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 312 (M+1); Rt = 4,68 min.

Example 110 (General procedure (B))

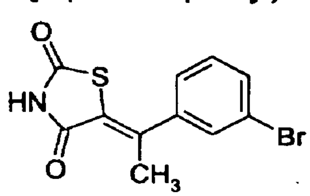
5-[1-(3-Fluoro-4-methoxyphenyl)ethylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 268 (M+1); Rt = 3,58 min.

Example 111 (General procedure (B))

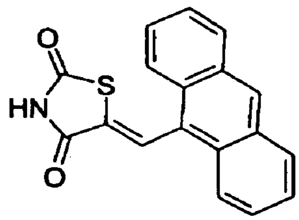
5-[1-(3-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,13 min.

Example 112 (General procedure (B))

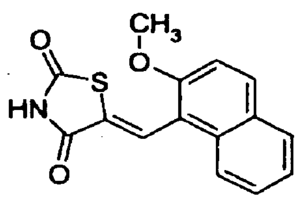
5-Anthracen-9-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 306 (M+1); Rt = 4,64 min.

Example 113 (General procedure (B))

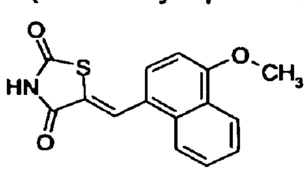
5-(2-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,02 min.

Example 114 (General procedure (B))

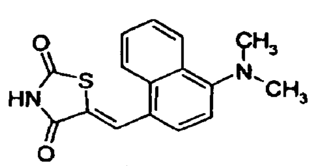
5-(4-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,31 min.

Example 115 (General procedure (B))

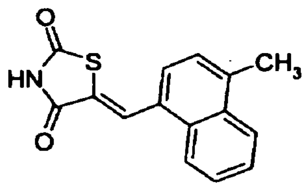
5-(4-Dimethylaminonaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 4,22 min.

Example 116 (General procedure (B))

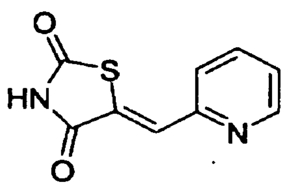
5-(4-Methylnaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,47 min.

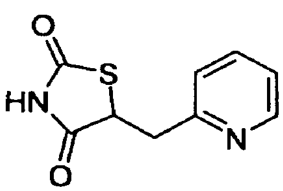
Example 117 (General procedure (B))

5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione



Example 118

5-Pyridin-2-ylmethyl-thiazolidine-2,4-dione

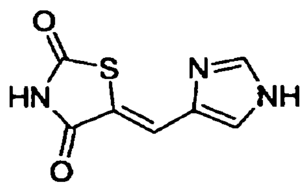


5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione (5 g) in tetrahydrofuran (300 ml) was added 10% Pd/C (1 g) and the mixture was hydrogenated at ambient pressure for 16 hours. More 10% Pd/C (5 g) was added and the mixture was hydrogenated at 50 psi for 16 hours. After filtration and evaporation *in vacuo*, the residue was purified by column chromatography eluting with a mixture of ethyl acetate and heptane (1:1). This afforded the title compound (0.8 g, 16%) as a solid.

TLC: R_f = 0.30 (SiO_2; EtOAc: heptane 1:1)

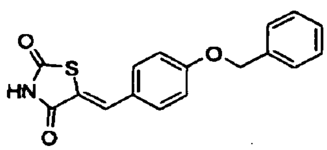
Example 119 (General procedure (B))

5-(1H-Imidazol-4-ylmethylene)-thiazolidine-2,4-dione



Example 120 (General procedure (B))

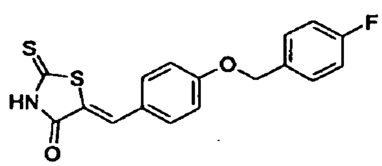
5-(4-Benzyloxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 6,43 min ; 99 % (2A)

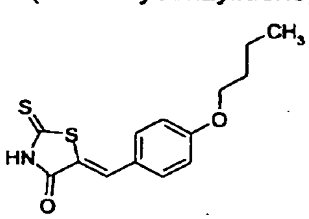
Example 121 (General procedure (B))

5-[4-(4-Fluorobenzyloxy)benzylidene]-2-thioxothiazolidin-4-one



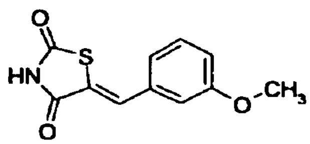
Example 122 (General procedure (B))

5-(4-Butoxybenzylidene)-2-thioxothiazolidin-4-one



Example 123 (General procedure (B))

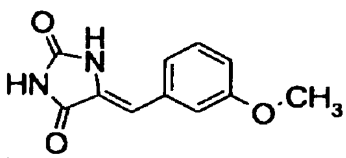
5-(3-Methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 236 (M+1); Rt = 4,97 min

Example 124 (General procedure (B))

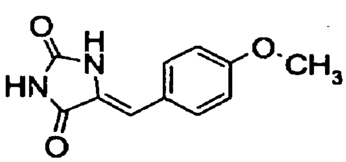
5-(3-Methoxybenzylidene)imidazolidine-2,4-dione



HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.43 min.

Example 125 (General procedure (B))

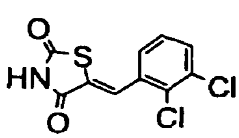
5-(4-Methoxybenzylidene)imidazolidine-2,4-dione



HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.38 min.

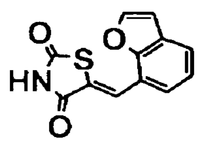
Example 126 **(General procedure (B))**

5-(2,3-Dichlorobenzylidene)thiazolidine-2,4-dione



Example 127 **(General procedure (B))**

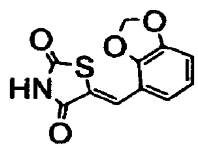
5-Benzofuran-7-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4,57 min.

Example 128 **(General procedure (B))**

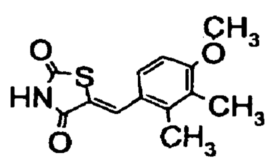
5-Benzo[1,3]dioxol-4-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 250 (M+1); Rt = 4,00 min.

Example 129 **(General procedure (B))**

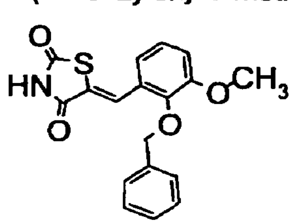
5-(4-Methoxy-2,3-dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 264 (M+1); Rt = 5,05 min.

Example 130 **(General procedure (B))**

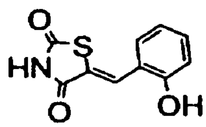
5-(2-Benzyloxy-3-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 5,14 min.

Example 131 **(General procedure (B))**

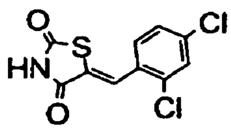
5-(2-Hydroxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 222 (M+1); Rt = 3,67 min.

Example 132 **(General procedure (B))**

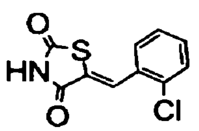
5-(2,4-Dichlorobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.60 (2H, "s"), 7.78 (1H, s), 7.82 (1H, s).

Example 133 **(General procedure (B))**

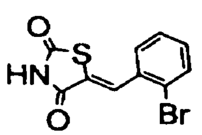
5-(2-Chlorobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.40 (1H, t), 7.46 (1H, t), 7.57 (1H, d), 7.62 (1H, d), 7.74 (1H, s).

Example 134 **(General procedure (B))**

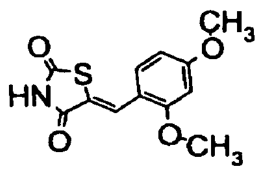
5-(2-Bromobenzylidene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): 7.33 (1H, t), 7.52 (1H, t), 7.60 (1H, d), 7.71 (1H, s), 7.77 (1H, d).

Example 135 **(General procedure (B))**

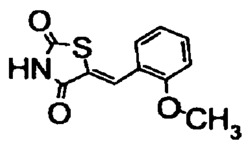
5-(2,4-Dimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 266 (M+1) Rt = 4,40 min.

Example 136 **(General procedure (B))**

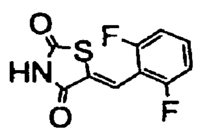
5-(2-Methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 236 (M+1); Rt = 4,17 min.

Example 137 **(General procedure (B))**

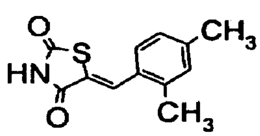
5-(2,6-Difluorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 242 (M+1); Rt = 4,30 min.

Example 138 **(General procedure (B))**

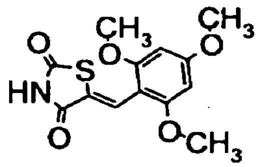
5-(2,4-Dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 234 (M+1); Rt = 5,00 min.

Example 139 **(General procedure (B))**

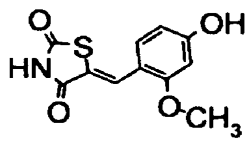
5-(2,4,6-Trimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 296 (M+1); Rt = 4,27 min.

Example 140 **(General procedure (B))**

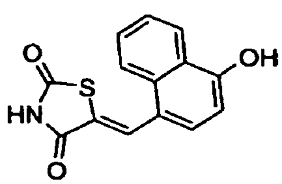
5-(4-Hydroxy-2-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 252 (M+1); Rt = 3,64 min.

Example 141 **(General procedure (B))**

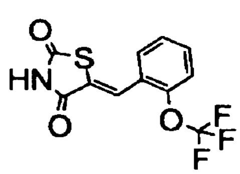
5-(4-Hydroxynaphthalen-1-ylmethylene)thiazolidine-2,4-dione



^{1}H-NMR (DMSO-d_6): δ = 7.04 (1H, d), 7.57 (2H, m), 7.67 (1H, t), 8.11 (1H, d), 8.25 (1H, d), 8.39 (1H, s) 11.1 (1H, s), 12.5 (1H, bs). HPLC-MS (Method C): m/z: 272 (M+1); Rt = 3.44 min.

Example 142 **(General procedure (B))**

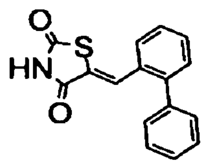
5-(2-Trifluoromethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 290 (M+1); Rt = 4,94 min.

Example 143 **(General procedure (B))**

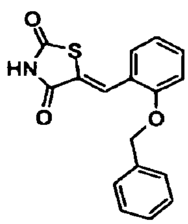
5-Biphenyl-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 282 (M+1); Rt = 5,17 min.

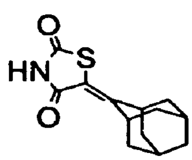
*Example 144 **(General procedure (B))***

5-(2-Benzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 312 (M+1); Rt = 5,40 min.

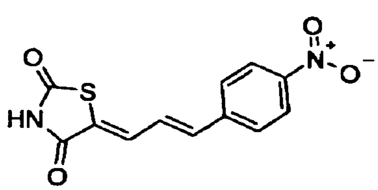
Example 145 **(General procedure (B))** 5-Adamantan-2-ylidenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 4,30 min.

Example 146 (General Procedure (B))

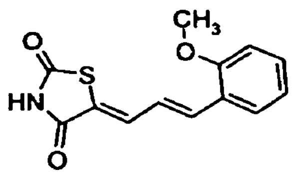
5-[3-(4-Nitrophenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 277 (M+1); Rt = 3.63 min.

Example 147 (General Procedure (B))

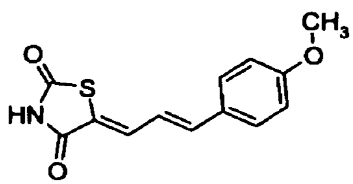
5-[3-(2-Methoxyphenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.81 min.

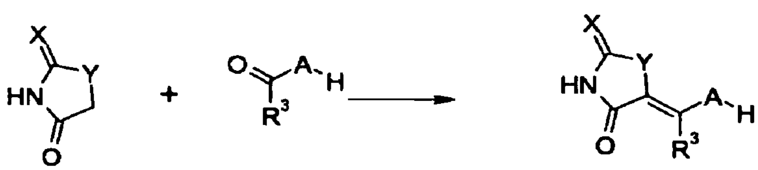
Example 148 (General Procedure (B))

5-[3-(4-Methoxyphenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.67 min.

General procedure (C) for preparation of compounds of general formula I_2:



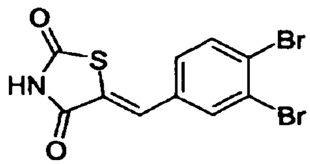
I_2

wherein X, Y, A, and R^3 are as defined above and A is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} as defined above.

This general procedure (C) is quite similar to general procedure (B) and is further illustrated in the following example:

Example 149 (General procedure (C))

5-(3,4-Dibromobenzylidene)thiazolidine-2,4-dione



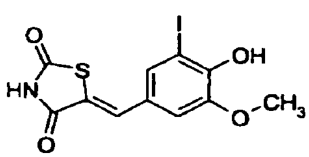
A mixture of thiazolidine-2,4-dione (90%, 65 mg, 0.5 mmol), 3,4-dibromobenzaldehyde (132 mg, 0.5 mmol), and piperidine (247 µL, 2.5 mmol) was shaken in acetic acid (2 mL) at 110 °C for 16 hours. After cooling, the mixture was concentrated to dryness *in vacuo* . The resulting crude product was shaken with water, centrifuged, and the supernatant was discarded. Subsequently the residue was shaken with ethanol, centrifuged, the supernatant was discarded and the residue was further evaporated to dryness to afford the title compound.

^{1}H NMR (Acetone-d_6): δ_H 7.99 (d,1H), 7.90 (d,1H), 7.70 (s,1H), 7.54 (d,1H); HPLC-MS (Method A): m/z: 364 (M+1); Rt = 4.31 min.

The compounds in the following examples were similarly prepared. Optionally, the compounds can be further purified by filtration and washing with water instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by preparative HPLC.

Example 150 (General procedure (C))

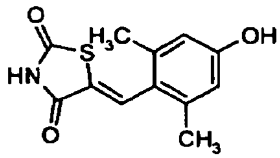
5-(4-Hydroxy-3-iodo-5-methoxybenzylidene)thiazolidine-2,4-dione



Mp = 256 °C; ^{1}H NMR (DMSO-d_6) δ = 12.5 (s,broad,1H), 10.5 (s,broad,1H), 7.69 (s,1H), 7.51 (d,1H), 7.19 (d,1H)3.88 (s,3H), ^{13}C NMR (DMSO-d_6) δ_C = 168.0, 167.7 , 149.0, 147.4, 133.0, 131.2, 126.7, 121.2, 113.5, 85.5, 56.5; HPLC-MS (Method A): m/z: 378 (M+1); Rt = 3.21 min.

Example 151 (General procedure (C))

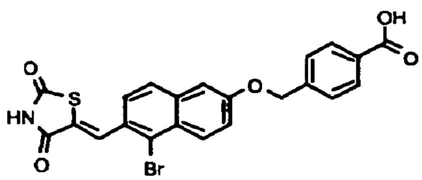
5-(4-Hydroxy-2,6-dimethylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 250 (M+1); Rt.= 2.45 min.

Example 152 (General procedure (C))

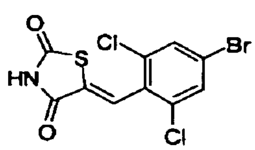
4-[5-Bromo-6-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-2-yloxymethyl]-benzoic acid



HPLC-MS (Method C): m/z: 506 (M+23); Rt.= 4.27 min.

Example 153 (General procedure (C))

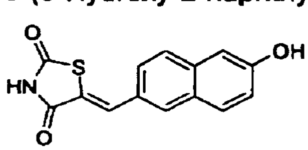
5-(4-Bromo-2,6-dichlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 354 (M+1); Rt.= 4.36 min.

Example 154 (General procedure (C))

5-(6-Hydroxy-2-naphthylmethylene) thiazolidine-2,4-dione



Mp 310-314 °C, ^1H NMR (DMSO-d_6): δ_H = 12.5 (s,broad,1H), 8.06(d,1H), 7.90-7.78(m,2H),7.86 (s,1H), 7.58 (dd,1H),7.20 7.12 (m,2H). ^{13}C NMR (DMSO-d_6): δ_C = 166.2, 165.8 , 155.4, 133.3, 130.1, 129.1, 128.6, 125.4, 125.3, 125.1, 124.3, 120.0, 117.8, 106.8; HPLC-MS (Method A): m/z: 272 (M+1); Rt = 3.12 min.

Preparation of the starting material, 6-hydroxy-2-naphtalenecarbaldehyde:

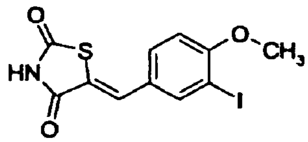
6-Cyano-2-naphthalenecarbaldehyde (1.0 g, 5.9 mmol) was dissolved in dry hexane (15 mL) under nitrogen. The solution was cooled to -60 °C and a solution of diisobutyl aluminium hydride (DIBAH) (15 mL, 1M in hexane) was added dropwise. After the addition, the solution was left at room temperature overnight. Saturated ammonium chloride solution (20 mL) was added and the mixture was stirred at room temperature for 20 min, subsequently aqueous H_2SO_4 (10% solution, 15 mL) was added followed by water until all salt was dissolved. The resulting solution was extracted with ethyl acetate (3x), the combined organic phases were dried with $MgSO_4$, evaporated to dryness to afford 0.89 g of 6-hydroxy-2-naphtalenecarbaldehyde.

Mp.: 153.5-156.5 °C; HPLC-MS (Method A): m/z: 173 (M+1); Rt = 2.67 min; ^1H NMR (DMSO-d_6): δ_H = 10.32(s,1H), 8.95 (d,1H), 10.02 (s,1H), 8.42 (s,broad,1H), 8.01 (d,1H), 7.82-7.78 (m,2H), 7.23-7.18 (m,2H).

Alternative preparation of 6-hydroxy-2-naphtalenecarbaldehyde:
To a stirred cooled mixture of 6-bromo-2-hydroxynaphthalene (25.3 g, 0.113 mol) in THF (600 mL) at -78 °C was added n-BuLi (2.5 M, 100 mL, 0.250 mol) dropwise. The mixture turned yellow and the temperature rose to –64 °C. After ca 5 min a suspension appeared. After addition, the mixture was maintained at –78 °C. After 20 minutes, a solution of DMF (28.9 mL, 0.373 mol) in THF (100 mL) was added over 20 minutes. After addition, the mixture was allowed to warm slowly to room temperature. After 1 hour, the mixture was poured in ice/water (200 mL). To the mixture citric acid was added to a pH of 5. The mixture was stirred for 0.5 hour. Ethyl acetate (200 mL) was added and the organic layer was separated and washed with brine (100 mL), dried over Na_2SO_4 and concentrated. To the residue was added heptane with 20% ethyl acetate (ca 50 mL) and the mixture was stirred for 1 hour. The mixture was filtered and the solid was washed with ethyl acetate and dried *in vacuo* to afford 16 g of <u>the title compound</u>.

Example 155 (General procedure (C))

5-(3-Iodo-4-methoxybenzylidene)thiazolidiene-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H 12.55 (s,broad,1H), 8.02 (d,1H), 7.72 (s,1H), 7.61 (d,1H)7.18(d,1H), 3.88 (s,3H); ^{13}C NMR (DMSO-d_6): δ_C 168.1, 167.7 , 159.8, 141.5, 132.0, 130.8, 128.0, 122.1, 112.5, 87.5, 57.3. HPLC-MS (Method A): m/z: 362 (M+1); Rt = 4.08 min.

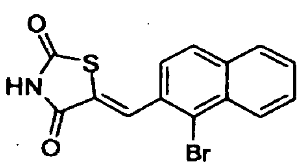
Preparation of the starting material, 3-iodo-4-methoxybenzaldehyde:

4-Methoxybenzaldehyde (0.5 g, 3.67 mmol) and silver trifluoroacetate (0.92 g, 4.19 mmol) were mixed in dichloromethane (25 mL). Iodine (1.19 g, 4.7 mmol) was added in small portions and the mixture was stirred overnight at room temperature under nitrogen. The mixture was subsequently filtered and the residue washed with DCM. The combined filtrates were treated with an acqueous sodium thiosulfate solution (1 M) until the colour disappeared. Subsequent extraction with dichloromethane (3 x 20 mL) followed by drying with $MgSO_4$ and evaporation *in vacuo* afforded 0.94 g of 3-iodo-4-methoxybenzaldehyde.

Mp 104-107 °C; HPLC-MS (Method A): m/z:263 (M+1); Rt = 3.56 min.;^{1}H NMR ($CDCl_3$): δ_H = 8.80 (s,1H), 8.31 (d,1H), 7.85 (dd,1H) 6.92 (d,1H), 3.99 (s, 3H).

Example 156 (General procedure (C))

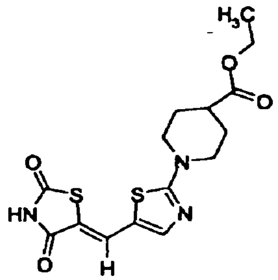
5-(1-Bromonaphthalen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: =336 (M+1); Rt = 4.46 min.

Example 157 (General procedure (C))

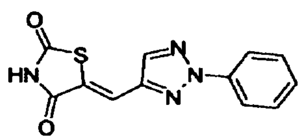
1-[5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiazol-2-yl]piperidine-4-carboxylic acid ethyl ester



^{1}H NMR (DMSO-d_6): δ_H = 7.88 (s,1H), 7.78 (s,1H), 4.10 (q,2H), 4.0-3.8 (m,2H), 3.40-3.18 (m,2H), 2.75-2.60 (m,1H), 2.04-1.88 (m,2H), 1.73-1.49 (m,2H), 1.08 (t,3H); HPLC-MS (Method A): m/z: 368 (M+1); Rt = 3.41 min.

Example 158 (General procedure (C))

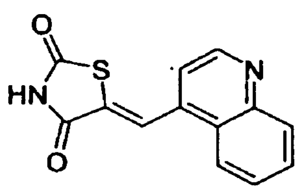
5-(2-Phenyl-[1,2,3]triazol-4-ylmethylene) thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.6 (s,broad,1H), 8.46 (s,1H), 8.08 (dd,2H), 7.82 (s,1H), 7.70-7.45 (m, 3H). HPLC-MS (Method A): m/z: 273 (M+1); Rt = 3.76 min.

Example 159 (General procedure (C))

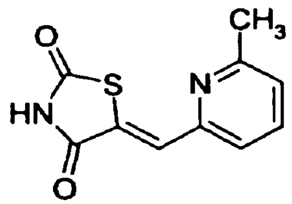
5-(Quinolin-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 2.40 min.

Example 160 (General procedure (C))

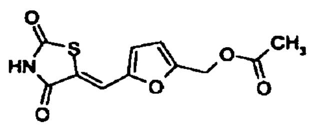
5-(6-Methylpyridin-2-ylmethylene)thiazolidine-2,4-dione



^1H NMR (DMSO-d_6): δ_H = 12.35 (s,broad,1H), 7.82 (t,1H), 7.78 (s,1H), 7.65 (d,1H), 7.18 (d,1H), 2.52 (s,3 H); HPLC-MS (Method A): m/z: 221 (M+1); Rt = 3.03 min.

Example 161 (General procedure (C))

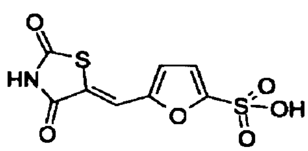
5-(2,4-dioxothiazolidin-5-ylidenemethyl)-furan-2-ylmethylacetate



^1H NMR (DMSO-d_6): δ_H = 12.46 (s,broad,1H), 7.58 (s,1H), 7.05 (d,1H), 6.74 (s,1H), 5.13 (s,2H), 2.10 (s,3H). HPLC-MS (Method A): m/z: 208 (M-CH_3COO); Rt = 2.67 min.

Example 162 (General procedure (C))

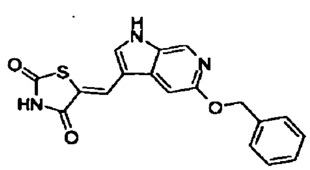
5-(2,4-Dioxothiazolidin-5-ylidenemethyl)furan-2-sulfonic acid



HPLC-MS (Method A): m/z:276 (M+1); Rt = 0.98 min.

Example 163 (General procedure (C))

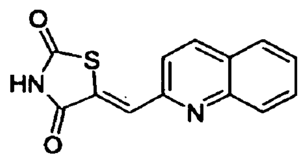
5-(5-Benzyloxy-1H-pyrrolo[2,3-c]pyridin-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 352 (M+1); Rt = 3.01 min.

Example 164 (General procedure (C))

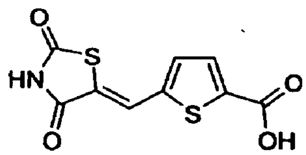
5-(Quinolin-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 3.40 min.

Example 165 (General procedure (C))

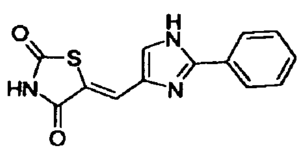
5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiophene-2-carboxylic acid



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 1.96 min.

Example 166 (General procedure (C))

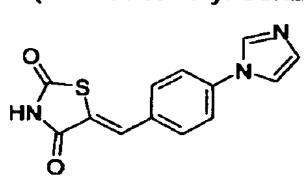
5-(2-Phenyl-1H-imidazol-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 2.89 min.

Example 167 (General procedure (C))

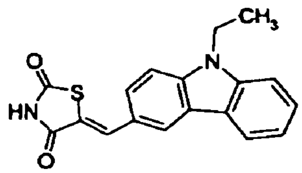
5-(4-Imidazol-1-yl-benzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 1.38 min.

Example 168 (General procedure (C))

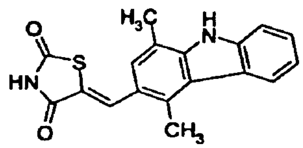
5-(9-Ethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.52 min.

Example 169 (General procedure (C))

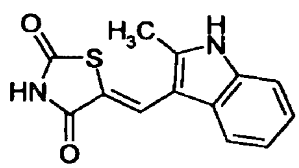
5-(1,4-Dimethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.35 min.

Example 170 (General procedure (C))

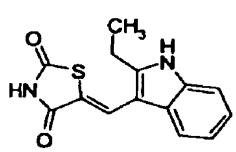
5-(2-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.24 min.

Example 171 (General procedure (C))

5-(2-Ethylindol-3-ylmethylene)thiazolidine-2,4-dione



2-Methylindole (1.0 g, 7.6mmol) dissolved in diethyl ether (100 mL) under nitrogen was treated with n-Butyl lithium (2 M in pentane, 22.8 mmol) and potassium *tert*-butoxide (15.2

mmol) with stirring at RT for 30 min. The temperature was lowered to –70 C and methyl iodide (15.2 mmol) was added and the resulting mixture was stirred at –70 for 2 h. Then 5 drops of water was added and the mixture allowed to warm up to RT. Subsequently, the mixture was poured into water (300 mL), pH was adjusted to 6 by means of 1N hydrochloric acid and the mixture was extracted with diethyl ether. The organic phase was dried with Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel using heptane/ether(4/1) as eluent. This afforded 720 mg (69 %) of 2-ethylindole.

^{1}H NMR (DMSO-d_6): δ = 10.85 (1H,s); 7.39 (1H,d); 7.25 (1H,d); 6.98(1H,t); 6.90(1H,t); 6.10 (1H,s); 2.71 (2H,q); 1.28 (3H,t).

2-Ethylindole (0.5 g, 3.4mmol) dissolved in DMF (2 mL) was added to a cold (0 °C) premixed (30 minutes) mixture of DMF (1.15 mL) and phosphorous oxychloride (0.64 g, 4.16 mmol). After addition of 2-ethylindole, the mixture was heated to 40 °C for 1 h, water (5 mL) was added and the pH adjusted to 5 by means of 1 N sodium hydroxide.The mixture was subsequently extracted with diethyl ether, the organic phase isolated, dried with $MgSO_4$ and evaporated to dryness affording 2-ethylindole-3-carbaldehyde (300 mg).

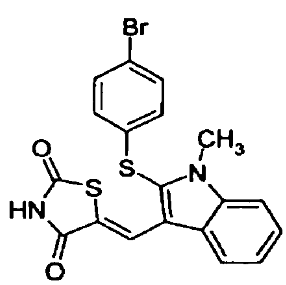
HPLC-MS (Method C): m/z:174 (M+1); Rt. =2.47 min.

2-Ethylindole-3-carbaldehyde (170 mg) was treated with thiazolidine-2,4-dione using the general procedure (C) to afford the title compound (50 mg).

HPLC-MS (Method C):m/z: 273 (M+1); Rt.= 3.26 min.

Example 172 (General procedure (C))

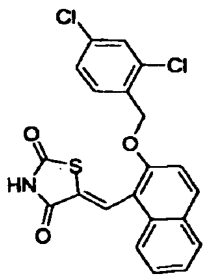
5-[2-(4-Bromophenylsulfanyl)-1-methyl-1H-indol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 447 (M+1); Rt = 5.25 min.

Example 173 (General procedure (C))

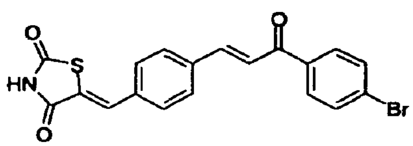
5-[2-(2,4-Dichlorobenzyloxy)-naphthalen-1-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): (anyone 1) m/z: 430 (M+1); Rt = 5.47 min.

Example 174 (General procedure (C))

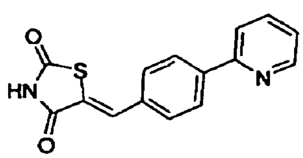
5-{4-[3-(4-Bromophenyl)-3-oxopropenyl]-benzylidene}thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 416 (M+1); Rt = 5.02 min.

Example 175 (General procedure (C))

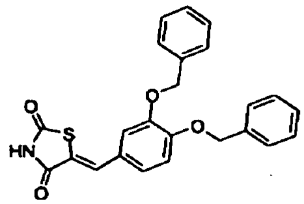
5-(4-Pyridin-2-ylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 283 (M+1), Rt = 2.97 min.

Example 176 (General procedure (C))

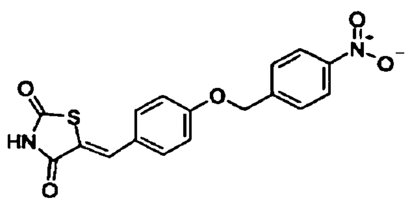
5-(3,4-Bisbenzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 418 (M+1); Rt = 5.13 min.

Example 177 (General procedure (C))

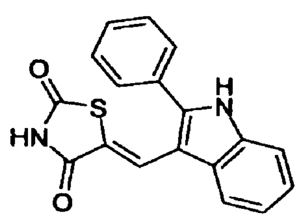
5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.45 min.

Example 178 (General procedure (C))

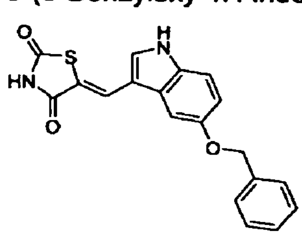
5-(2-Phenyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 321 (M+1); Rt = 3.93 min.

Example 179 (General procedure (C))

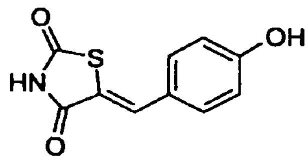
5-(5-Benzyloxy-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 351 (M+1); Rt = 4.18 min.

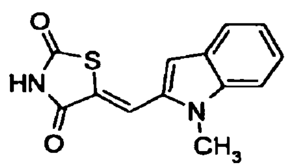
Example 180 (General procedure (C))

5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione



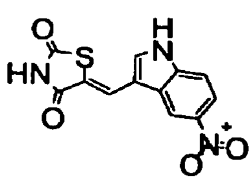
HPLC-MS (Method A): m/z: 222 (M+1); Rt = 2.42 min.

Example 181 **(General procedure (C))** 5-(1-Methyl-1H-indol-2-ylmethylene)thiazolidine-2,4-dione



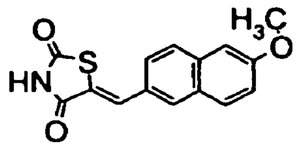
^{1}H NMR (DMSO-d_6): δ_H = 12.60 (s,broad,1H), 7.85 (s,1H), 7.68 (dd,1H), 7.55 (dd,1H), 7.38 (dt,1H), 7.11 (dt,1H) 6.84 (s,1H), 3.88 (s,3H); HPLC-MS (Method A): m/z: 259 (M+1); Rt = 4.00 min.

Example 182 **(General procedure (C))** 5-(5-Nitro-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



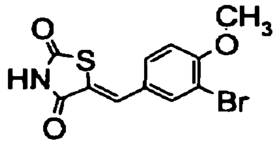
.Mp 330-333 °C, ^{1}H NMR (DMSO-d_6): δ_H = 12.62 (s,broad,1H), 8.95 (d,1H), 8.20 (s,1H), 8.12 (dd,1H), 7.98 (s,broad,1H), 7.68 (d,1H); HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.18 min.

Example 183 **(General procedure (C))** 5-(6-Methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione



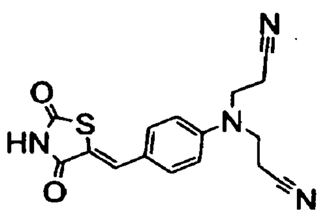
HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4.27 min.

Example 184 **(General procedure (C))** 5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione



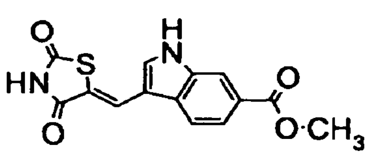
HPLC-MS (Method A): m/z: 314 (M+1), Rt = 3.96 min.

Example 185 ***(General procedure (C))*** 3-{(2-Cyanoethyl)-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]amino}propionitrile



HPLC-MS (Method A): m/z: 327 (M+1); Rt = 2.90 min.

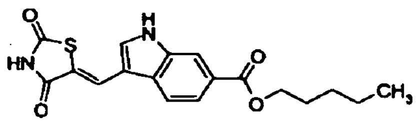
Example 186 ***(General procedure (C))*** 3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 3.22-3-90 min.

Example 187

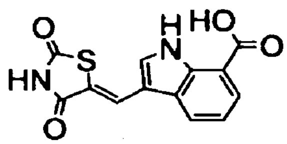
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid pentyl ester.



3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester (example 186, 59 mg; 0.195mmol) was stirred in pentanol (20 mL) at 145 °C for 16 hours. The mixture was evaporated to dryness affording the title compound (69 mg).

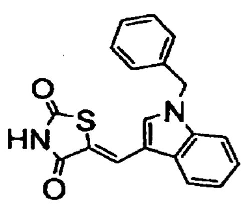
HPLC-MS (Method C): m/z: 359 (M+1); Rt.= 4.25 min.

Example 188 **(General procedure (C))** 3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carboxylic acid



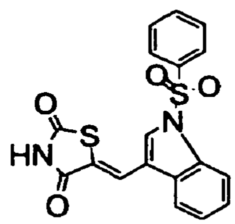
HPLC-MS (Method A): m/z: 289 (M+1); Rt = 2.67 min.

Example 189 **(General procedure (C))** 5-(1-Benzylindol-3-ylmethylene)thiazolidine-2,4-dione



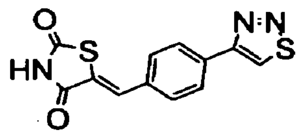
HPLC-MS (Method A): m/z: 335 (M+1); Rt = 4.55 min.

Example 190 **(General procedure (C))** 5-(1-Benzenesulfonylindol-3-ylmethylene)thiazolidine-2,4-dione



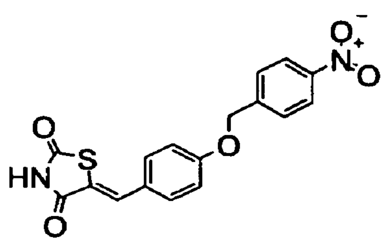
HPLC-MS (Method A): m/z: = 385 (M+1); Rt = 4.59 min.

Example 191 **(General procedure (C))** 5-(4-[1,2,3]Thiadiazol-4-ylbenzylidene)thiazolidine-2,4-dione



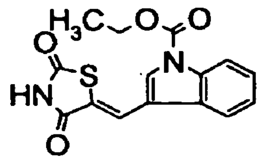
HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.45 min.

Example 192 **(General procedure (C))** 5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



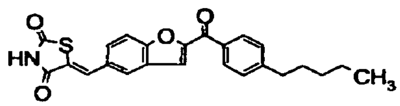
HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.42 min.

Example 193 **(General procedure (C))** 3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-1-carboxylic acid ethyl ester



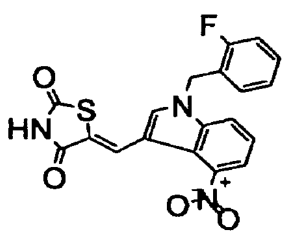
HPLC-MS (Method A): m/z: 317 (M+1); Rt = 4.35 min.

Example 194 **(General procedure (C))** 5-[2-(4-Pentylbenzoyl)-benzofuran-5-ylmethylene]thiazolidine-2,4-dione



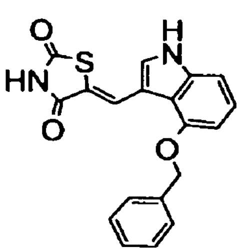
HPLC-MS (Method A): m/z: 420 (M+1); Rt = 5.92 min.

Example 195 **(General procedure (C))** 5-[1-(2-Fluorobenzyl)-4-nitroindol-3-ylmethylene]thiazolidine-2,4-dione



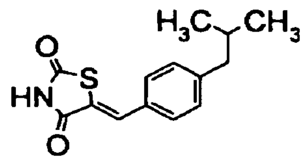
HPLC-MS (Method A): (Anyone 1) m/z: 398 (M+1); Rt = 4.42 min.

Example 196 **(General procedure (C))** 5-(4-Benzyloxyindol-3-ylmethylene)thiazolidine-2,4-dione



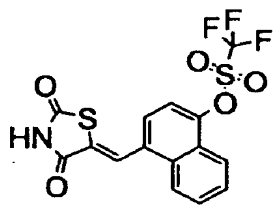
HPLC-MS (Method A): m/z: 351 (M+1); Rt = 3.95 min.

Example 197 **(General procedure (C))** 5-(4-Isobutylbenzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 262 (M+1); Rt = 4.97 min.

Example 198 **(General procedure (C))** Trifluoromethanesulfonic acid 4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yl ester

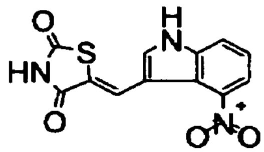


HPLC-MS (Method A): m/z: 404 (M+1); Rt = 4.96 min.

Preparation of starting material:

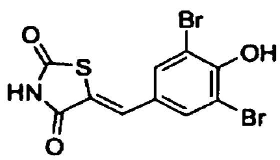
4-Hydroxy-1-naphthaldehyde (10 g, 58 mmol) was dissolved in pyridin (50 ml) and the mixture was cooled to 0-5 °C. With stirring, trifluoromethanesulfonic acid anhydride (11.7 ml, 70 mmol) was added drop-wise. After addition was complete, the mixture was allowed to warm up to room temperature, and diethyl ether (200 ml) was added. The mixture was washed with water (2 x 250 ml), hydrochloric acid (3N, 200 ml), and saturated aqueous sodium chloride (100 ml). After drying (MgSO4), filtration and concentration in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 8.35 g (47%) trifluoromethanesulfonic acid 4-formylnaphthalen-1-yl ester, mp 44-46.6 °C.

Example 199 **(General procedure (C))** 5-(4-Nitroindol-3-ylmethylene)-thiazolidine-2,4-dione

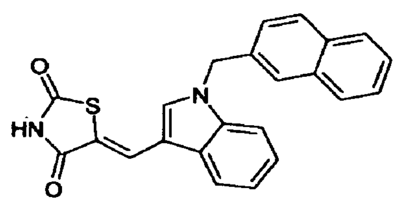


HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.14 min.

Example 200 **(General procedure (C))** 5-(3,5-Dibromo-4-hydroxy-benzylidene)thiazolidine-2,4-dione



^{1}H NMR (DMSO-d_6): δ_H = 12.65 (broad,1H), 10.85 (broad,1H), 7.78 (s,2H), 7.70 (s,1H); HPLC-MS (Method A): m/z: 380 (M+1); Rt = 3.56 min.



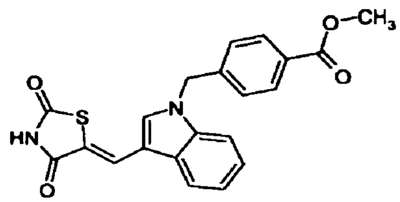
Example 201 **(General procedure (C))**

HPLC-MS (Method A): m/z: 385 (M+1); Rt = 5.08 min.

General procedure for preparation of starting materials for examples 201 - 204:
Indole-3-carbaldehyde (3.8 g, 26 mmol) was stirred with potassium hydroxide (1.7 g) in acetone (200 mL) at RT until a solution was obtained indicating full conversion to the indole potassium salt. Subsequently the solution was evaporated to dryness *in vacuo*. The residue was dissolved in acetone to give a solution containing 2.6 mmol/20 mL.

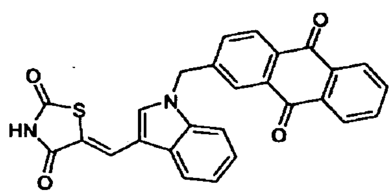
20 mL portions of this solution were mixed with equimolar amounts of arylmethylbromides in acetone (10 mL). The mixtures were stirred at RT for 4 days and subsequently evaporated to dryness and checked by HPLC-MS. The crude products, 1-benzylated indole-3-carbaldehydes, were used for the reaction with thiazolidine-2,4-dione using the general procedure C.

Example 202 **(General procedure (C))** 4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]benzoic acid methyl ester



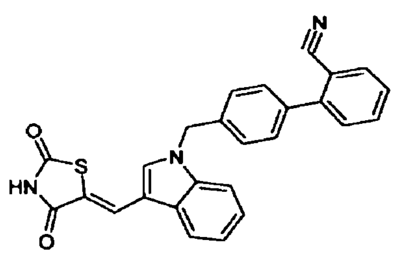
HPLC-MS (Method A): m/z: 393 (M+1); Rt = 4.60 min.

Example 203 **(General procedure (C))** 5-[1-(9,10-Dioxo-9,10-dihydroanthracen-2-ylmethyl)-1*H*-indol-3-ylmethylene]thiazolidine-2,4-dione



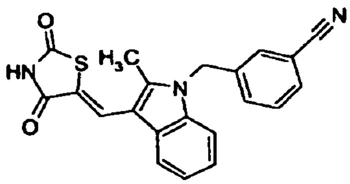
HPLC-MS (Method A): m/z: 465 (M+1); Rt = 5.02 min.

Example 204 **(General procedure (C))** 4'-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]biphenyl-2-carbonitrile



HPLC-MS (Method A): m/z: 458 (M+23); Rt = 4.81 min.

Example 205 **(General procedure (C))**
3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzonitrile.

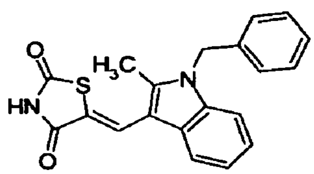


2-Methylindole-3-carbaldehyde (200 mg, 1.26 mmol) was added to a slurry of 3-bromomethylbenzenecarbonitrile (1.26 mmol) followed by sodium hydride, 60%, (1.26 mmol) in DMF (2 mL). The mixture was shaken for 16 hours, evaporated to dryness and washed with water and ethanol. The residue was treated with thiazolidine-2,4-dione following the general procedure C to afford the title compound (100 mg).

HPLC-MS (Method C): m/z: 374 (M+1); Rt. = 3.95 min.

Example 206 **(General procedure (C))**

5-(1-Benzyl-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.

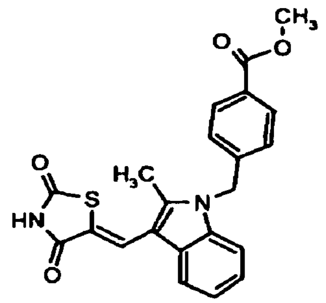


This compound was prepared in analogy with the compound described in example 205 from benzyl bromide and 2-methylindole-3-carbaldehyde, followed by reaction with thiazolidine-2,4-dione resulting in 50 mg of the title compound.

HPLC-MS (Method C): m/z: 349 (M+1); Rt. = 4.19 min.

Example 207

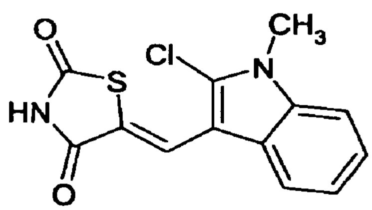
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzoic acid methyl ester



This compound was prepared in analogy with the compound described in example 205 from 4-(bromomethyl)benzoic acid methyl ester and 2-methylindole-3-carbaldehyde, followed by reaction with thiazolidine-2,4-dione.

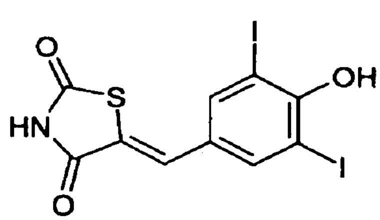
HPLC-MS (Method C): m/z: 407 (M+1); Rt.= 4.19 min.

Example 208 **(General procedure (C))** 5-(2-Chloro-1-methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 293 (M+1); Rt = 4.10 min.

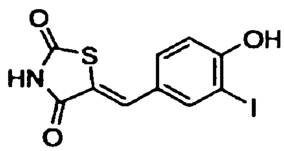
Example 209 **(General procedure (C))** 5-(4-Hydroxy-3,5-diiodo-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 474 (M+1); Rt = 6.61 min.

Example 210 **(General procedure (C))**

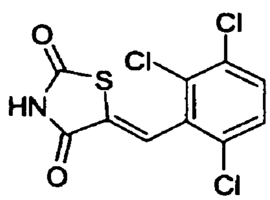
5-(4-Hydroxy-3-iodobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 348 (M+1); Rt. = 3.13 min

^{1}H-NMR: (DMSO-d_6): 11.5 (1H,broad); 7.95(1H,d); 7.65(1H,s); 7.45 (1H,dd); 7.01(1H,dd); 3.4 (1H,broad).

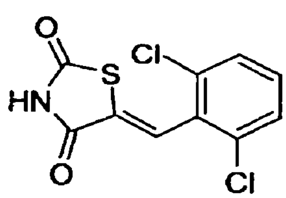
Example 211 **(General procedure (C))**5-(2,3,6-Trichlorobenzylidene)thiazolidine-2,4-dione



H PLC-MS (Method C): m/z: 309 (M+1); Rt.= 4.07 min

Example 212 **(General procedure (C))**

5-(2,6-Dichlorobenzylidene)thiazolidine-2,4-dione



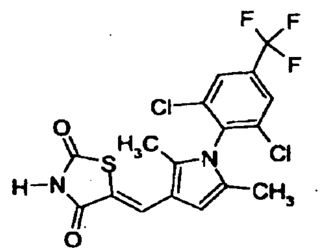
Mp. 152-154°C.

HPLC-MS (Method C): m/z: 274 (M+1), Rt.= 3.70 min

^{1}H-NMR: (DMSO-d_6): 12.8 (1H, broad); 7.72 (1H,s); 7.60 (2H,d); 7.50 (1H,t).

Example 213 **(General procedure (C))**

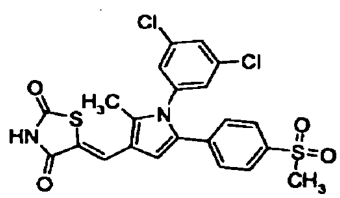
5-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-2,5-dimethyl-1*H*-pyrrol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 436 (M+1); Rt. 4.81 min

Example 214 **(General procedure (C))**

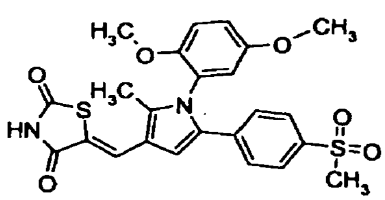
5-[1-(3,5-Dichlorophenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 508 (M+1); Rt. = 4.31 min

Example 215 **(General procedure (C))**

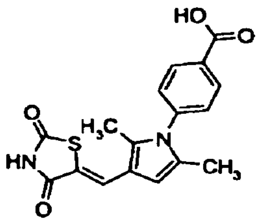
5-[1-(2,5-Dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 499 (M+1); Rt. = 3.70 min

Example 216 **(General procedure (C))**

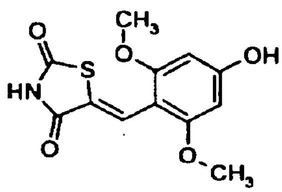
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2,5-dimethylpyrrol-1-yl]benzoic acid



HPLC-MS (Method C): m/z:342 (M+1); Rt.= 3.19 min

Example 217 **(General procedure (C))**

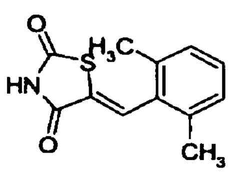
5-(4-Hydroxy-2,6-dimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z:282(M+1); Rt.= 2.56, mp=331-333 °C

Example 218 **(General procedure (C))**

5-(2,6-Dimethylbenzylidene)thiazolidine-2,4-dione

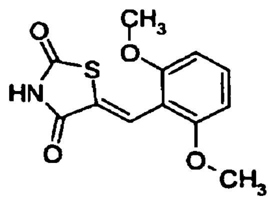


M.p: 104-105 °C

HPLC-MS (Method C): m/z: 234 (M+1); Rt.= 3.58 min,

Example 219 **(General procedure (C))**

5-(2,6-Dimethoxybenzylidene)thiazolidine-2,4-dione

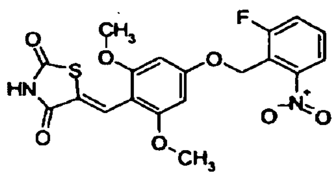


Mp: 241-242 °C

HPLC-MS (Method C): m/z: 266 (M+1); Rt.= 3.25 min;

Example 220 **(General procedure (C))**

5-[4-(2-Fluoro-6-nitrobenzyloxy)-2,6-dimethoxybenzylidene]thiazolidine-2,4-dione

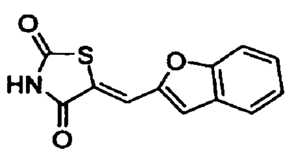


Mp: 255-256 °C

HPLC-MS (Method C): m/z: 435 (M+1), Rt 4.13 min,

Example 221 **(General procedure (C))**

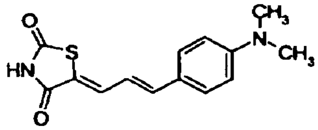
5-Benzofuran-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z:246 (M+1); Rt.= 3.65 min, mp = 265-266 °C .

Example 222 **(General procedure (C))**

5-[3-(4-Dimethylaminophenyl)allylidene]thiazolidine-2,4-dione

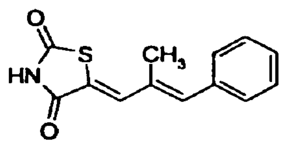


HPLC-MS (Method C): m/z:276(M+1); Rt.= 3.63, mp = 259-263 °C

^{1}H-NMR: (DMSO-d_6) δ= 12.3 (1H,broad); 7.46 (2H,d); 7.39 (1H,d); 7.11 (1H,d); 6.69 (2H,d); 6.59 (1H, dd); 2.98 (3H,s).

Example 223 **(General procedure (C))**

5-(2-Methyl-3-phenylallylidene)thiazolidine-2,4-dione

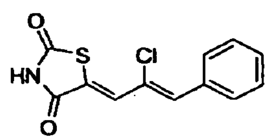


Mp: 203-210 °C

HPLC-MS (Method C): m/z: 246 (M+1); Rt = 3.79 min.

Example 224 **(General procedure (C))**

5-(2-Chloro-3-phenylallylidene)thiazolidine-2,4-dione

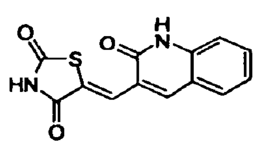


Mp: 251-254 °C

HPLC-MS (Method C): m/z: 266 (M+1; Rt = 3.90 min

Example 225 **(General procedure (C))**

5-(2-Oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione

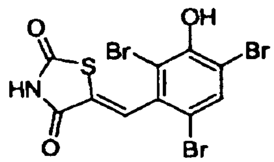


Mp: 338-347 °C

HPLC-MS (Method C): m/z: 273 (M+1); Rt. = 2.59 min.

Example 226 **(General procedure (C))**

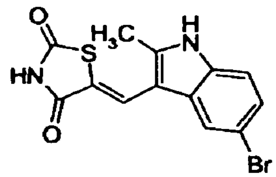
5-(2,4,6-Tribromo-3-hydroxybenzylidene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 459 (M+1);Rt.= 3.65 min.

Example 227 **(General procedure (C))**

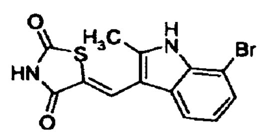
5-(5-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 339 (M+1); Rt = 3.37min.

Example 228 **(General procedure (C))**

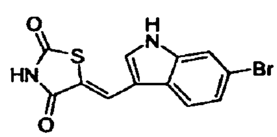
5-(7-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 319 (M+1); Rt = 3.48min.

Example 229 **(General procedure (C))**

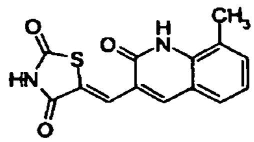
5-(6-Bromoindol-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 325 (M+1); Rt = 3.54 min.

Example 230 **(General procedure (C))**

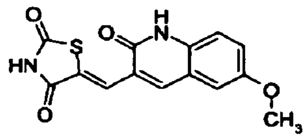
5-(8-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 287 (M+1); Rt = 2.86 min.

Example 231 **(General procedure (C))**

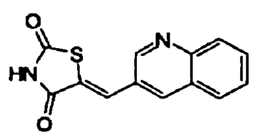
5-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 303 (M+1); Rt = 2.65 min.

Example 232 **(General procedure (C))**

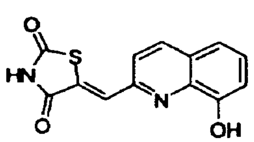
5-Quinolin-3-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 2.77 min.

Example 233 **(General procedure (C))**

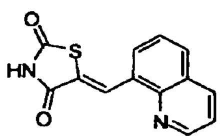
5-(8-Hydroxyquinolin-2-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 273 (M+1); Rt = 3.44 min.

Example 234 **(General procedure (C))**

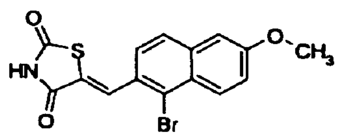
5-Quinolin-8-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 3.15 min.

Example 235 **(General procedure (C))**

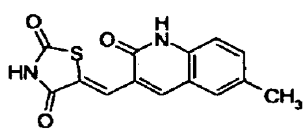
5-(1-Bromo-6-methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 366 (M+1); Rt = 4.44 min.

Example 236 **(General procedure (C))**

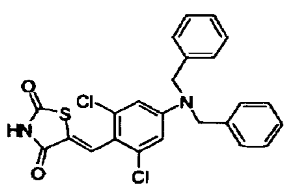
5-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 287 (M+1); Rt. = 2.89 min.

Example 237 **(General procedure (D))**

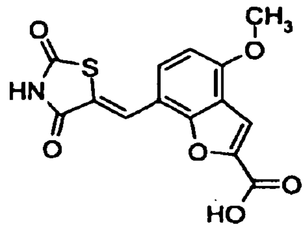
5-(2,6-Dichloro-4-dibenzylaminobenzylidene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 469 (M+1); Rt = 5.35 min.

Example 238 (General Procedure (C))

7-(2,4-Dioxothiazolidin-5-ylidenemethyl)-4-methoxybenzofuran-2-carboxylic acid



HPLC-MS (Method C): m/z: 320 (M+1); Rt = 2.71 min.

Preparation of the intermediate, 7-formyl-4-methoxybenzofuran-2-carboxylic acid:

A mixture of 2-hydroxy-6-methoxybenzaldehyde (6.4 g, 42 mmol), ethyl bromoacetate (14.2 mL, 128 mmol) and potassium carbonate (26 g, 185 mmol) was heated to 130 ^{o}C. After 3 h the mixture was cooled to room temperature and acetone (100 mL) was added, the mixture was subsequently filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 7.5 g (55%) of ethyl 4-methoxybenzofuran-2-carboxylate.

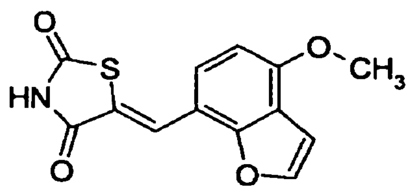
A solution of ethyl 4-methoxybenzofuran-2-carboxylate (6.9 g, 31.3 mmol) in dichloromethane (70 ml) was cooled to 0 ^{o}C and a solution of titanium tetrachloride (13.08 g, 69 mmol) was added drop wise. After 10 minutes dichloromethoxymethane (3.958 g, 34 mmol) was added over 10 minutes. After addition, the mixture was warmed to room temperature for 18 hours and the mixture poured into hydrochloric acid (2N, 100 mL). The mixture was stirred for 0.5 hour and then extracted with a mixture of ethyl acetate and toluene (1:1). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 5.8 g (80%) of ethyl 7-formyl-4-methoxybenzofuran-2-carboxylate.

7-formyl-4-methoxybenzofuran-2-carboxylate (5.0 g, 21.5 mmol) and sodium carbonate (43 mmol) in water (100 mL) was refluxed until a clear solution appeared (about 0.5 hour). The solution was filtered and acidified to pH =1 with hydrochloric acid (2 N), the resulting product was filtered off and washed with ethyl acetate and ethanol and dried to afford 3.5 g (74%) of 7-formyl-4-methoxybenzofuran-2-carboxylic acid as a solid.

^{1}H NMR (DMSO-d_6): δ = 10.20 (s, 1H) ; 8.07 (d, 1H) ; 7.70 (s, 1H) ; 7.17 (d, 1H) ; 4.08 (s, 3H).

Example 239 (General Procedure (C))

5-(4-Methoxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 267 (M+1); Rt = 3.30 min.

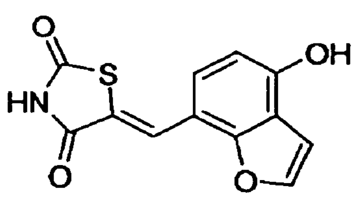
Preparation of the intermediate, 4-methoxybenzofuran-7-carbaldehyde:

A mixture of 7-formyl-4-methoxybenzofuran-2-carboxylic acid (3.0 g, 13.6 mmol) and Cu (0.6 g, 9.44 mmol) in quinoline (6 mL) was refluxed. After 0.5 h the mixture was cooled to room temperature and water (100 mL) and hydrochloric acid (10 N, 20 mL) were added. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), filtered through celite and the organic layer separated and washed with a sodium carbonate solution, dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.5 g crude product. Column chromatography SiO_2, EtOAc/heptanes=1/4 gave 1.1 g (46%) of 4-methoxybenzofuran-7-carbaldehyde as a solid.

^{1}H NMR ($CDCl_3$): δ: 10.30 (s,1H) ; 7.85 (d,1H) ; 7.75 (d,1H) ; 6.98 (d,1H) ; 6.87 (d,1H) ; 4.10 (s,3H). HPLC-MS (Method C) :m/z: 177 (M+1); Rt. = 7.65 min.

Example 240 (General Procedure (C))

5-(4-Hydroxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: = 262 (M+1); Rt 2.45 min.

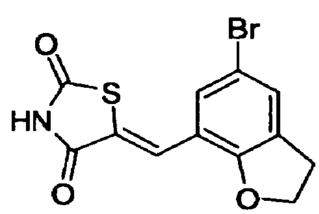
Preparation of the intermediate, 4-hydroxybenzofuran-7-carbaldehyde

A mixture of 4-methoxybenzofuran-7-carbaldehyde (1.6 g, 9.1 mmol) and pyridine hydrochloride (4.8 g, 41.7mmol) in quinoline (8 mL) was refluxed. After 8 h the mixture was cooled to room temperature and poured into water (100 mL) and hydrochloric acid (2 N) was added to pH = 2. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), washed with a sodium carbonate solution, dried with Na_2SO_4 and concentrated *in vacuo* to afford 0.8 g crude product. This was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and heptane (1:3). This afforded 250 mg of 4-hydroxybenzofuran-7-carbaldehyde as a solid.

^1H NMR (DMSO-d_6): δ = 11.35 (s, broad,1H) ; 10.15 (s, 1H) ; 8.05 (d, 1H) ; 7.75 (d, 1H) ; 7.10 (d, 1H); 6.83 (d, 1H). HPLC-MS (Method C): m/z: 163 (M+1); Rt. = 6.36 min.

Example 241 (General Procedure (C))

5-(5-Bromo-2,3-dihydrobenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 328 (M+1); Rt = 3.66 min.

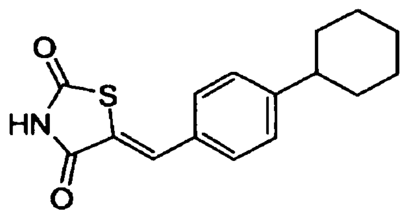
Preparation of the intermediate, 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde:
To a cooled (15 ^oC) stirred mixture dihydrobenzofuran (50.9 g, 0.424 mol) in acetic acid (500 mL), a solution of bromine (65.5 mL, 1.27 mol) in acetic acid (200 mL) was added drop wise over 1 hour. After stirring for 18 hours, a mixture of $Na_2S_2O_5$ (150 g) in water (250 mL) was added carefully, and the mixture was concentrated *in vacuo*. Water (200 mL) was added and the mixture was extracted with ethyl acetate containing 10% heptane, dried over Na_2SO_4 and concentrated *in vacuo* to give crude 5,7-dibromo-2,3-dihydrobenzofuran which was used as such for the following reaction steps. To a cooled solution (-78 ^oC) of crude 5,7-dibromo-2,3-dihydrobenzofuran (50.7 g, 0.182 mol) in THF (375 mL) a solution of n-BuLi (2.5 M, 80 mL, 0.200 mol) in hexane was added. After addition, the mixture was stirred for 20 min. DMF (16 mL) was then added drop wise at -78 ^oC. After addition, the mixture was stirred at room temperature for 3 h and then the mixture was poured into a mixture of ice water, (500 mL) and hydrochloric acid (10 N, 40 mL) and extracted with toluene, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on silica gel eluting with a mixture of ethyl

acetate and heptane (1:4) afforede 23 g of 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde as a solid.

^{1}H NMR ($CDCl_3$): δ:10.18 (s,1H) ; 7.75 (d,1H) ;7.55 (d,1H) ; 4.80 (t,2H) ; 3.28 (t,2H).

Example 242 (General Procedure (?))

5-(4-Cyclohexylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 288 (M+1); Rt = 5.03 min.

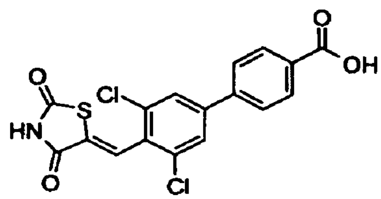
Preparation of the intermediate, 4-cyclohexylbenzaldehyde:

This compound was synthesized according to a modified literature procedure (*J. Org. Chem.*, **37**, No.24, (1972), 3972-3973). Cyclohexylbenzene (112.5 g, 0.702 mol) and hexamethylenetetramine (99.3 g, 0.708 mol) were mixed in TFA (375 mL). The mixture was stirred under nitrogen at 90 °C for 3 days. After cooling to room temperature the red-brown mixture was poured into ice-water (3600 ml) and stirred for 1 hour. The solution was neutralized with Na_2CO_3 (2 M solution in water) and extracted with dichloromethane (2.5 L). The organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The remaining red-brown oil was purified by fractional distillation to afford the title compound (51 g, 39%).

^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1H), 7.80 (d, 2H), 7.35 (d, 2H), 2.58 (m, 1H), 1.94-1.70 (m, 5 H), 1.51-1.17 (m, 5H)

Other ligands of the invention include

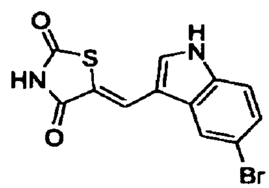
3',5'-Dichloro-4'-(2,4-dioxothiazolidin-5-ylidenemethyl)biphenyl-4-carboxylic acid:



The following compounds are commercially available and may be prepared using general procedures (B) and / or (C).

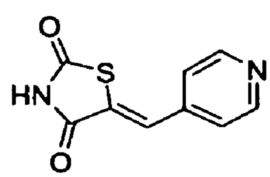
Example 243

5-(5-Bromo-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



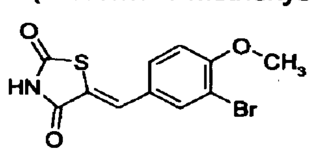
Example 244

5-Pyridin-4-ylmethylenethiazolidine-2,4-dione



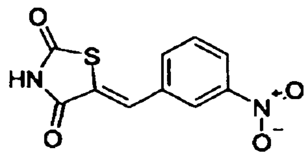
Example 245

5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione



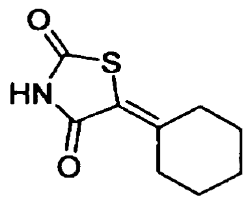
Example 246

5-(3-Nitrobenzylidene)thiazolidine-2,4-dione



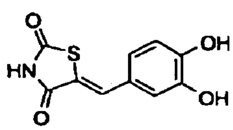
Example 247

5-Cyclohexylidene-1,3-thiazolidine-2,4-dione



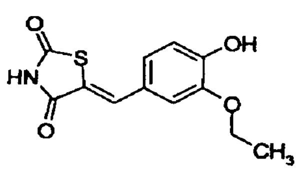
Example 248

5-(3,4-Dihydroxybenzylidene)thiazolidine-2,4-dione



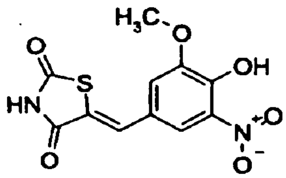
Example 249

5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione



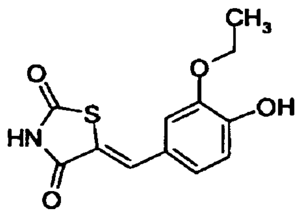
Example 250

5-(4-Hydroxy-3-methoxy-5-nitrobenzylidene)thiazolidine-2,4-dione



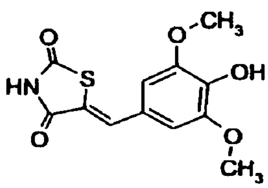
Example 251

5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione



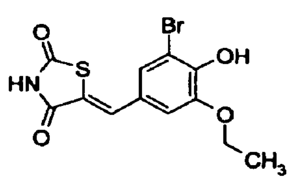
Example 252

5-(4-Hydroxy-3,5-dimethoxybenzylidene)thiazolidine-2,4-dione



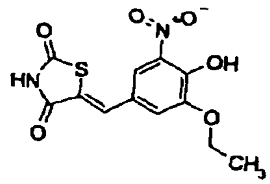
Example 253

5-(3-Bromo-5-ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione

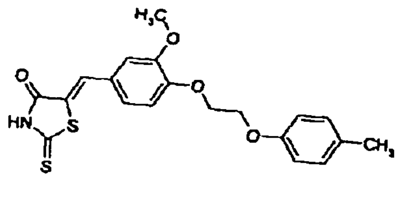


Example 254

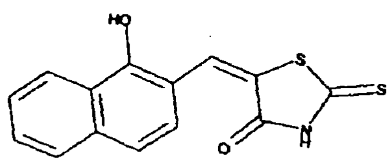
5-(3-Ethoxy-4-hydroxy-5-nitrobenzylidene)thiazolidine-2,4-dione



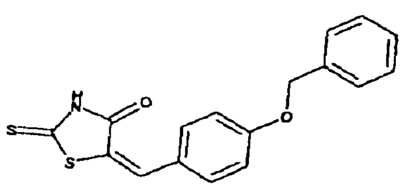
Example 255



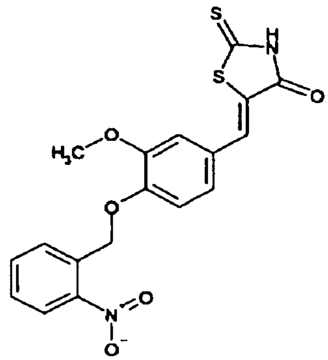
Example 256



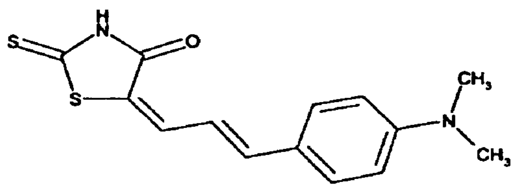
Example 257



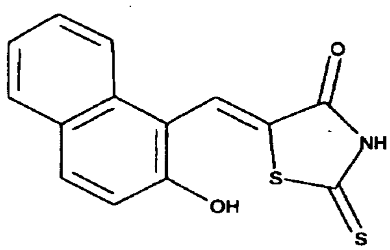
Example 258



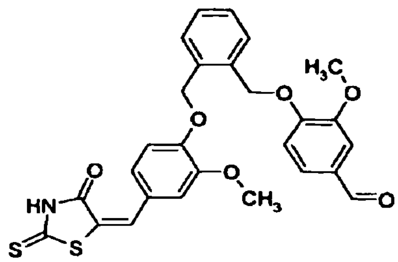
Example 259



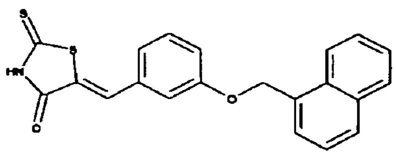
Example 260



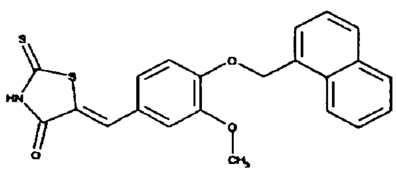
Example 261



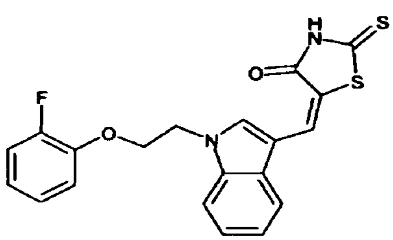
Example 262



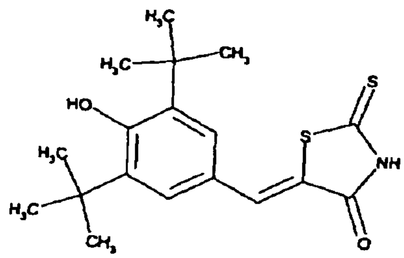
Example 263



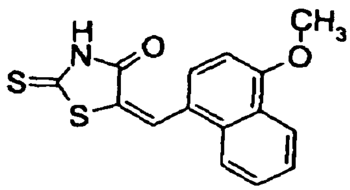
Example 264



Example 265

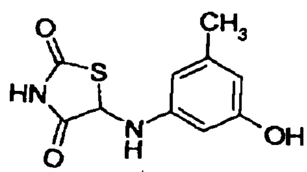


Example 266

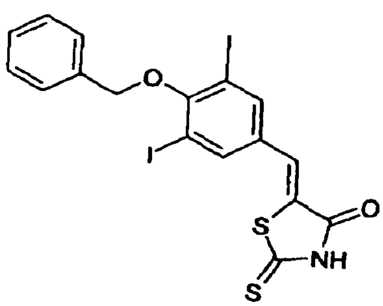


Example 267

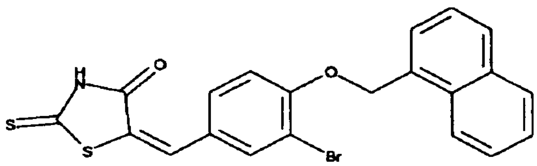
5-(3-Hydroxy-5-methyl-phenylamino)-thiazolidine-2,4-dione



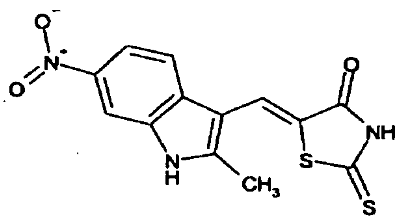
Example 268



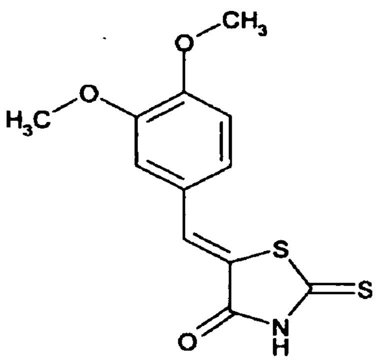
Example 269



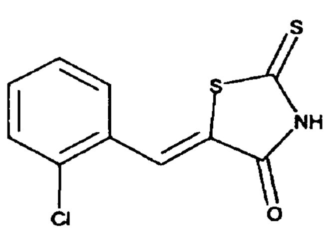
Example 270



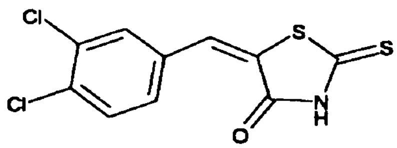
Example 271



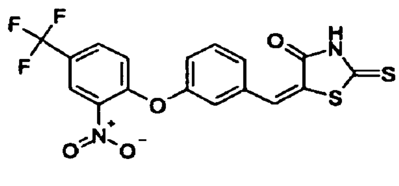
Example 272



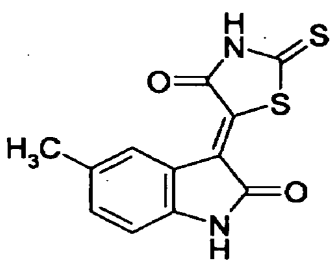
Example 273



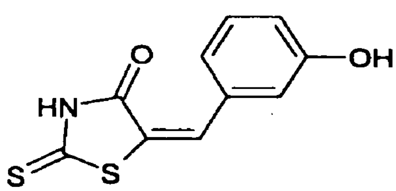
Example 274



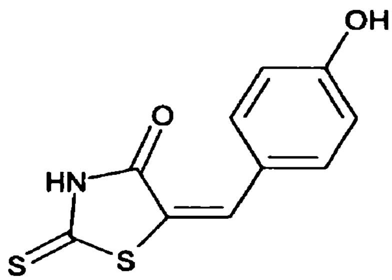
Example 275



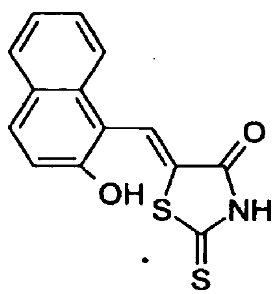
Example 276



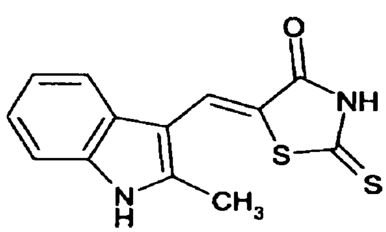
Example 277



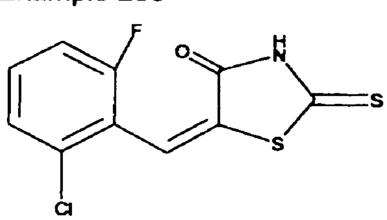
Example 278



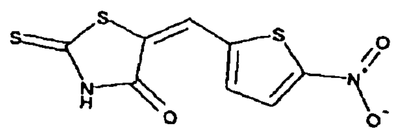
Example 279



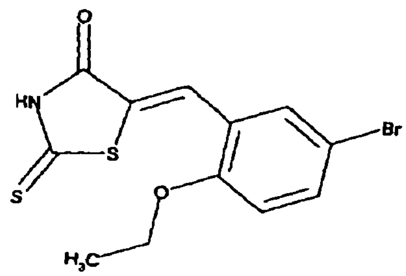
Example 280



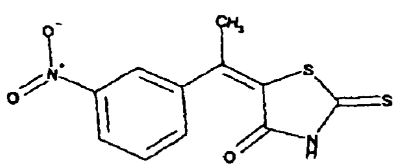
Example 281



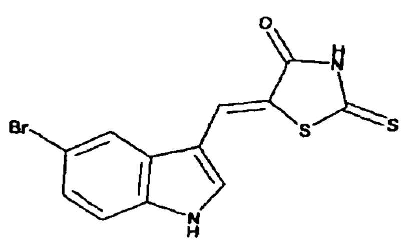
Example 282



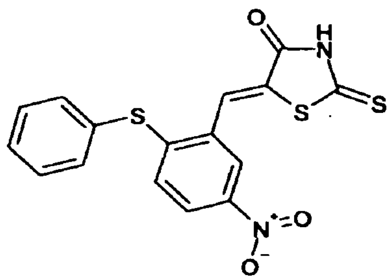
Example 283



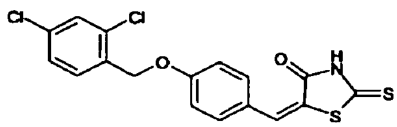
Example 284



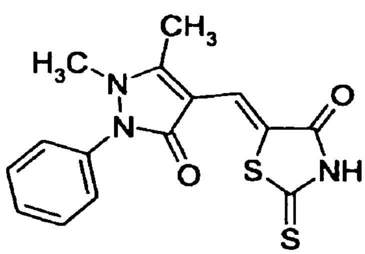
Example 285



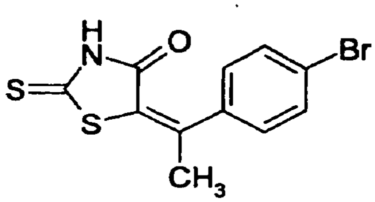
Example 286



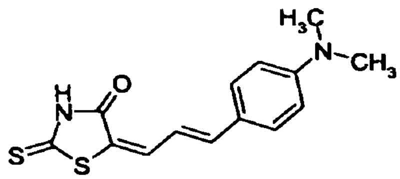
Example 287



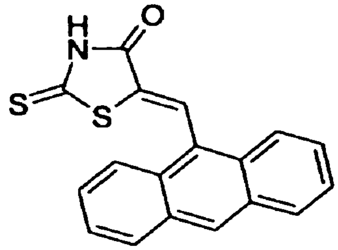
Example 288



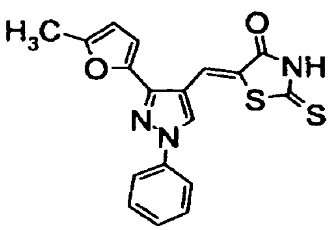
Example 289



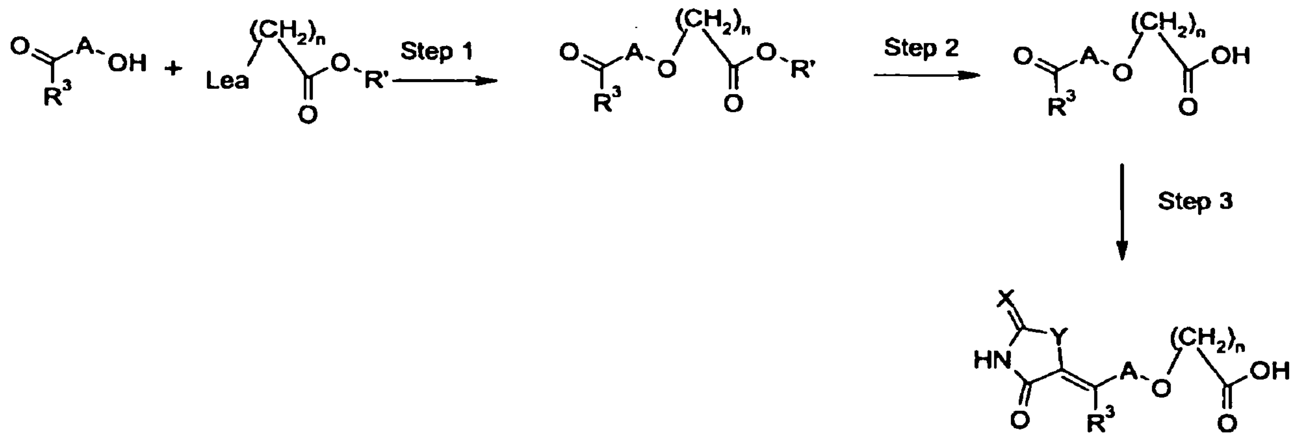
Example 290



Example 291



General procedure (D) for preparation of compounds of general formula I_3:



I_3

wherein X, Y, and R^3 are as defined above,

n is 1 or 3-20,

E is arylene or heterarylene (including up to four optional substituents, R^{13}, R^{14}, R^{15}, and R^{15A} as defined above),

R' is a standard carboxylic acid protecting group, such as C_1-C_8-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the like.

Step 1 is an alkylation of a phenol moiety. The reaction is preformed by reacting R^{10}-C(=O)-E-OH with an ω-bromo-alkane-carboxylic acid ester (or a synthetic equivalent) in the presence of a base such as sodium or potassium carbonate, sodium or potassium hydroxide, sodium hydride, sodium or potassium alkoxide in a solvent, such as DMF, NMP, DMSO, acetone, acetonitrile, ethyl acetate or isopropyl acetate. The reaction is performed at 20 – 160 °C, usually at room temperature, but when the phenol moiety has one or more substituents heating to 50 °C or more can be beneficial, especially when the substituents are in the ortho position relatively to the phenol. This will readily be recognised by those skilled in the art.

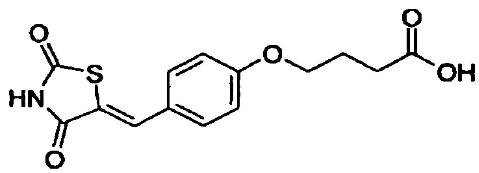
Step 2 is a hydrolysis of the product from step 1.

Step 3 is similar to general procedure (B) and (C).

This general procedure (D) is further illustrated in the following examples:

Example 292 (General procedure (D))

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



Step 1:

A mixture of 4-hydroxybenzaldehyde (9.21 g, 75 mmol), potassium carbonate (56 g, 410 mmol) and 4-bromobutyric acid ethyl ester (12.9 mL, 90 mmol) in *N,N*-dimethylformamide (250 mL) was stirred vigorously for 16 hours at room temperature. The mixture was filtered and concentrated *in vacuo* to afford 19.6 g (100%) of 4-(4-formylphenoxy)butyric acid ethyl ester as an oil. ^{1}H-NMR (DMSO-d_6): δ 1.21 (3H, t), 2.05 (2H, p), 2.49 (2H, t), 4.12 (4H, m), 7.13 (2H, d), 7.87 (2H, d), 9.90 (1H, s). HPLC-MS (Method A): m/z = 237 (M+1); R_t = 3.46 min.

Step 2:

4-(4-Formylphenoxy)butyric acid ethyl ester (19.6 g, 75 mmol) was dissolved in methanol (250 mL) and 1N sodium hydroxide (100 mL) was added and the resulting mixture was stirred at room temperature for 16 hours. The organic solvent was evaporated *in vacuo* (40 °C, 120 mBar) and the residue was acidified with 1N hydrochloric acid (110 mL). The mixture was filtered and washed with water and dried in vacuo to afford 14.3 g (91%) 4-(4-formylphenoxy)butyric acid as a solid. ^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.42 (2H, t), 4.13 (2H, t), 7.14 (2H, d), 7.88 (2H, d), 9.90 (1H, s), 12.2 (1H, bs). HPLC-MS (Method A): m/z = 209 (M+1); R_t = 2.19 min.

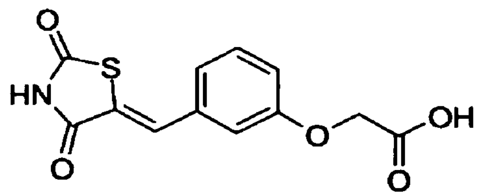
Step 3:

Thiazolidine-2,4-dione (3.55 g, 27.6 mmol), 4-(4-formylphenoxy)butyric acid (5.74 g, 27.6 mmol), anhydrous sodium acetate (11.3 g, 138 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying in vacuo afforded 2.74 g (32%) of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 1.97 (2H, p), 2.40 (2H, t), 4.07 (2H, t), 7.08 (2H, d), 7.56 (2H, d), 7.77 (1H, s), 12.2 (1H, bs), 12.5 (1H, bs); HPLC-MS (Method A): m/z: 308 (M+1); Rt = 2.89 min.

Example 293 (General procedure (D))

[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



Step 3:

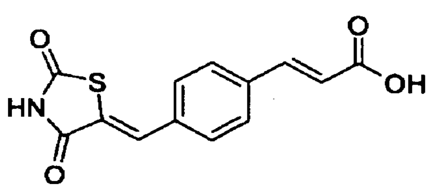
Thiazolidine-2,4-dione (3.9 g, 33 mmol), 3-formylphenoxyacetic acid (6.0 g, 33 mmol), anhydrous sodium acetate (13.6 g, 165 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying in vacuo afforded 5.13 g (56%) of [3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 4.69 (2H, s), 6.95 (1H, dd), 7.09 (1H, t), 7.15 (1H, d), 7.39 (1H, t),7.53 (1H, s); HPLC-MS (Method A): m/z = 280 (M+1) (poor ionisation); R_t = 2.49 min.

The compounds in the following examples were similarly prepared.

Example 294 (General procedure (D))

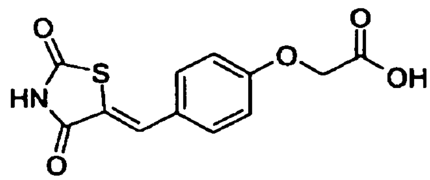
3-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acrylic acid



^{1}H-NMR (DMSO-d_6): δ 6.63 (1H, d), 7.59-7.64 (3H, m), 7.77 (1H, s), 7.83 (2H, m).

Example 295 (General procedure (D))

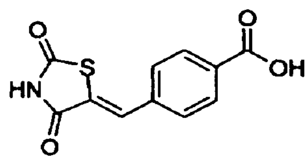
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



Triethylamine salt: ^{1}H-NMR (DMSO-d_6): δ 4.27 (2H, s), 6.90 (2H, d), 7.26 (1H, s), 7.40 (2H, d).

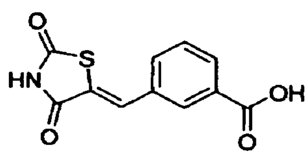
Example 296 (General procedure (D))

4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



Example 297 (General procedure (D))

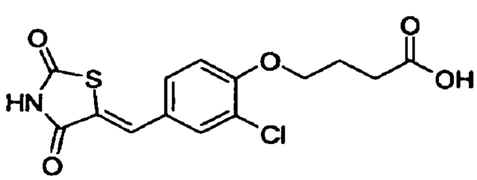
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



^{1}H-NMR (DMSO-d_6): δ 7.57 (1H, s), 7.60 (1H, t), 7.79 (1H, dt), 7.92 (1H, dt), 8.14 (1H, t).

Example 298 (General procedure (D))

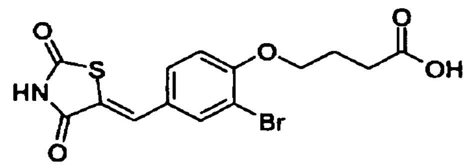
4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 2.00 (2H, p), 2.45 (2H, t), 4.17 (2H, t), 7.31 (1H, d), 7.54 (1H, dd), 7.69 (1H, d), 7.74 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 364 (M+23); Rt = 3.19 min.

Example 299 (General procedure (D))

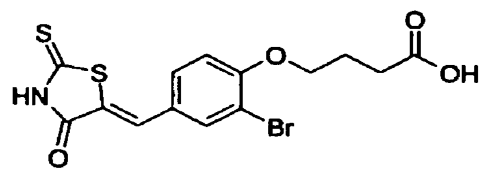
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.46 (2H, t), 4.17 (2H, t), 7.28 (1H, d), 7.57 (1H, dd), 7.25 (1H, s), 7.85 (1H, d), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3.35 min.

Example 300 (General procedure (D))

4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid

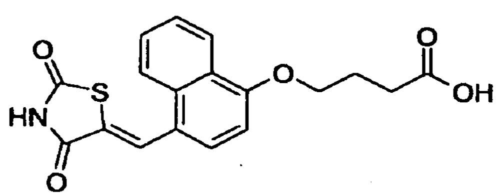


^{1}H-NMR (DMSO-d_6): δ 1.99 (2H, p), 2.45 (2H, t), 4.18 (2H, t), 7.28 (1H, d), 7.55 (1H, dd), 7.60 (1H, s), 7.86 (1H, d), 12.2 (1H, bs), 13.8 (1H, bs). HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3.84 min.

HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3,84 min

Example 301 (General procedure (D))

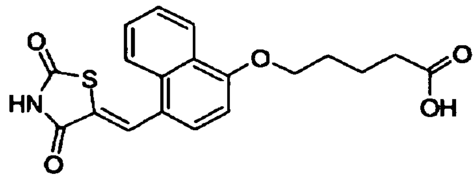
4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 2.12 (2H, p), 2.5 (below DMSO), 4.28 (2H, t), 7.12 (1H, d), 7.6-7.7 (3H, m), 8.12 (1H, d), 8.31 (1H, d), 8.39 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 380 (M+23); Rt = 3.76 min.

Example 302 **(General procedure (D))**

5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid

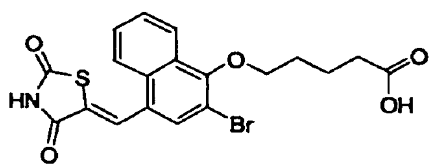


HPLC-MS (Method A): m/z: 394 (M+23); Rt = 3.62 min.

^{1}H-NMR (DMSO-d_6): δ 1.78 (2H, m), 1.90 (2H, m), 2.38 (2H, t), 4.27 (2H, t), 7.16 (1H, d), 7.6-7.75 (3H, m), 8.13 (1H, d), 8.28 (1H, d), 8.39 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs).

Example 303

5-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid.

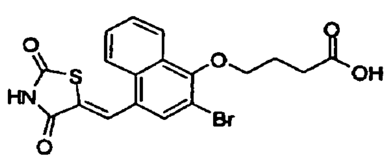


5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]pentanoic acid (example 302, 185 mg, 0.5 mmol) was treated with an equimolar amount of bromine in acetic acid (10 mL). Stirring at RT for 14 days followed by evaporation to dryness afforded a mixture of the brominated compound and unchanged starting material. Purification by preparative HPLC on a C18 column using acetonitrile and water as eluent afforded 8 mg of the title compound.

HPLC-MS (Method C): m/z: 473 (M+23), Rt. = 3.77 min

Example 304

4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid.

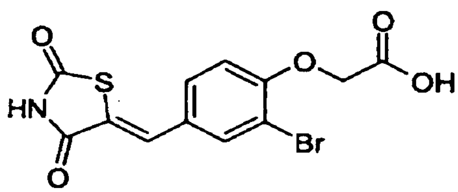


Starting with 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyric acid (example 301, 0.5 mmol) using the same method as in example 303 afforded 66 mg of the title compound.

HPLC-MS (Method C): m/z: 459 (M+23) ; Rt. = 3.59 min.

Example 305 (General procedure (D))

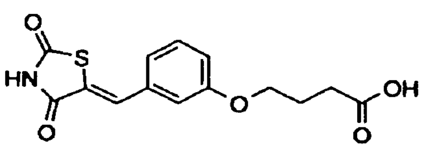
[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



^{1}H-NMR (DMSO-d_6): δ 4.90 (2H, s), 7.12 (1H, d), 7.52 (1H, dd), 7.65 (1H, s) 7.84 (1H, d).HPLC-MS (Method A): m/z: not observed; Rt = 2.89 min.

Example 306 (General procedure (D))

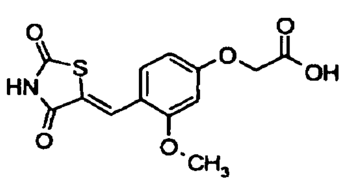
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



^{1}H-NMR (DMSO-d_6): δ 1.98 (2H, p), 2.42 (2H, t), 4.04 (2H, t), 7.05 (1H, dd), 7.15 (2H, m), 7.45 (1H, t), 7.77 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 330 (M+23); Rt = 3.05 min.

Example 307 **(General procedure (D))**

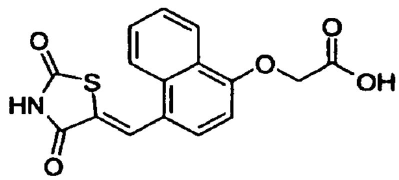
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-3-methoxyphenoxy]acetic acid



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 3,43 min.

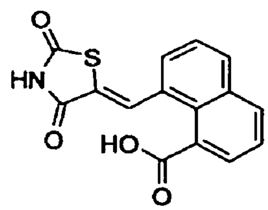
Example 308 **(General procedure (D))**

[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetic acid



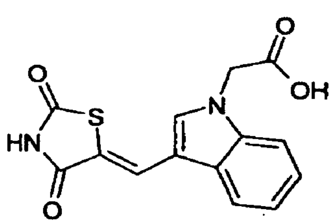
HPLC-MS (Method A): m/z: 330 (M+1); Rt = 3.25 min.

Example 309 **(General procedure (D))**8-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalene-1-carboxylic acid



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 2,49 min.

Example 310 **(General procedure (D))** [3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.90 min.

Preparation of starting material:

3-Formylindol (10 g, 69 mmol) was dissolved in *N,N*-dimethylformamide (100 mL) and under an atmosphere of nitrogenand with external cooling, keeping the temperature below 15 °C,

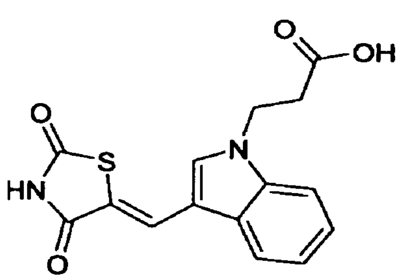
sodium hydride (60% in mineral oil, 3.0 g, 76 mmol) was added in portions. Then a solution of ethyl bromoacetate (8.4 mL, 76 mmol) in *N,N*-dimethylformamide (15 mL) was added dropwise over 30 minutes and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between water (300 mL) and ethyl acetate (2 x 150 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (100 mL), dried ($MgSO_4$) and concentrated in vacuo to afford 15.9 g (quant.) of (3-formylindol-1-yl)acetic acid ethyl ester as an oil.

^{1}H-NMR ($CDCl_3$): δ_H = 1.30 (3H, t), 4.23 (2H, q), 4.90 (2H, s), 7.3 (3H, m), 7.77 (1H, s), 8.32 (1H, d), 10.0 (1H, s).

(3-Formylindol-1-yl)acetic acid ethyl ester (15.9 g 69 mmol) was dissolved in 1,4-dioxane (100 mL) and 1N sodium hydroxide (10 mL) was added and the resulting mixture was stirred at room temperature for 4 days. Water (500 mL) was added and the mixture was washed with diethyl ether (150 mL). The aqueous phase was acidified with 5N hydrochloric acid and extracted with ethyl acetate (250 + 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford 10.3 g (73%) of (3-formylindol-1-yl)acetic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ_H = 5.20 (2H, s), 7.3 (2H, m), 7.55 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.95 (1H, s), 13.3 (1H, bs).

Example 311 **(General procedure (D))**3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]propionic acid



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.08 min.

Preparation of starting material:

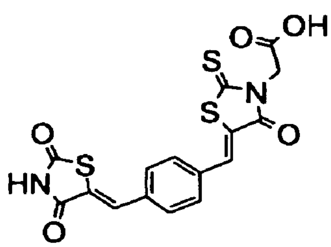
A mixture of 3-formylindol (10 g, 69 mmol), ethyl 3-bromopropionate (10.5 mL, 83 mmol) and potassium carbonate (28.5 g, 207 mmol) and acetonitrile (100 mL) was stirred vigorously at refux temperature for 2 days. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo* to afford 17.5 g (quant.) of 3-(3-formylindol-1-yl)propionic acid ethyl ester as a solid.

^{1}H-NMR (DMSO-d_6): δ_H = 1.10 (3H, t), 2.94 (2H, t), 4.02 (2H, q), 4.55 (2H, t), 7.3 (2H, m), 7.67 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.90 (1H, s).

3-(3-Formylindol-1-yl)propionic acid ethyl ester (17.5 g 69 mmol) was hydrolysed as described above to afford 12.5 g (83%) of 3-(3-formylindol-1-yl)propionic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ_H = 2.87 (2H, t), 4.50 (2H, t), 7.3 (2H, m), 7.68 (1H, d), 8.12 (1H, d), 8.31 (1H, s), 9.95 (1H, s), 12.5 (1H, bs).

Example 312 **(General procedure (D))**{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid

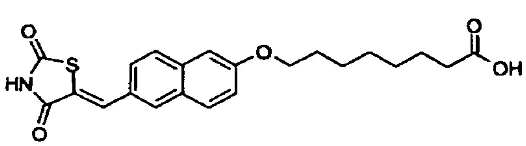


HPLC-MS (Method A): m/z: 429 (M+23); Rt = 3.89 min.

.

Example 313 **(General procedure (D))**

6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxyoctanoic acid



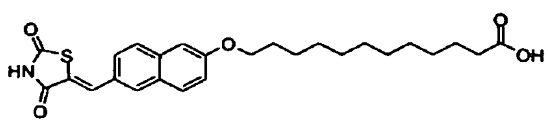
HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.36 min

The intermediate aldehyde for this compound was prepared by a slightly modified procedure: 6-Hydroxynaphthalene-2-carbaldehyde (1.0 g, 5.8 mmol) was dissolved in DMF (10 mL) and sodium hydride 60% (278 mg) was added and the mixture stirred at RT for 15 min. 8-Bromooctanoic acid (0.37 g, 1.7 mmol) was converted to the sodium salt by addition of sodium hydride 60% and added to an aliquot (2.5 mL) of the above naphtholate solution and the resulting mixture was stirred at RT for 16 hours. Aqueous acetic acid (10 %) was added and the mixture was extracted 3 times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and evaporated to dryness affording 300 mg of 8-(6-formylnaphthalen-2-yloxy)octanoic acid.

HPLC-MS (Method C): m/z 315 (M+1); Rt. = 4.24 min.

Example 314 **(General procedure (D))**

12-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]dodecanoic acid.

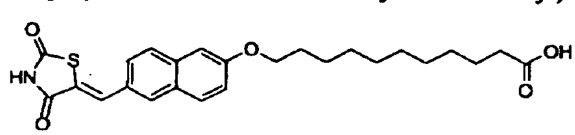


HPLC-MS (Method C): m/z: 492 (M+23); Rt.= 5.3 min.

The intermediate aldehyde was prepared similarly as described in example 313.

Example 315 **(General procedure (D))**

11-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]undecanoic acid.

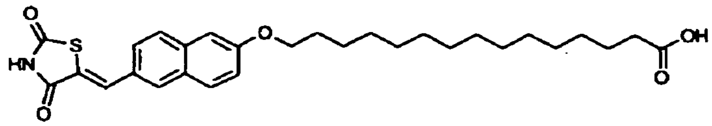


HPLC-MS (Method C): m/z:478 (M+23); Rt.= 5.17 min.

The intermediate aldehyde was prepared similarly as described in example 313.

Example 316 **(General procedure (D))**

15-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]pentadecanoic acid.

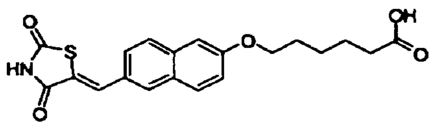


HPLC-MS (Method C): m/z: 534 (M+23); Rt.= 6.07 min.

The intermediate aldehyde was prepared similarly as described in example 313.

Example 317 **(General procedure (D))**

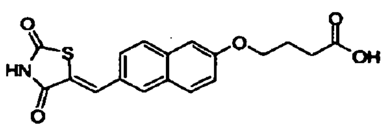
6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 3.71 min.

Example 318 **(General procedure (D))**

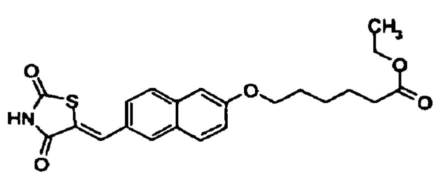
4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid.



HPLC-MS (Method C): m/z: 380 (M+23); Rt.= 3.23 min.

Example 319 **(General procedure (D))**

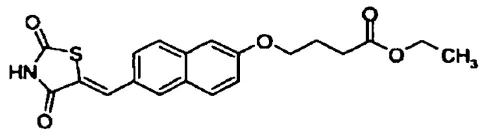
6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid ethyl ester.



HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.64 min.

Example 320 **(General procedure (D))**

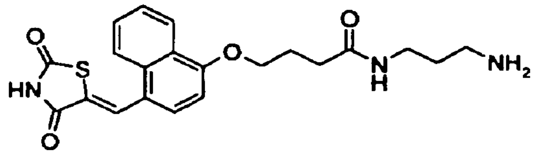
4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid ethyl ester.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 4.28 min.

Example 321

N-(3-Aminopropyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyramide



To a mixture of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid (example 301, 5.9 g, 16.5 mmol) and 1-hydroxybenzotriazole (3.35 g, 24.8 mmol) in DMF (60 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.75 g, 24.8 mmol) and the resulting mixture was stirred at room temperature for 2 hours. *N*-(3-amino-propylcarbamic acid *tert*-butyl ester (3.45 g, 19.8 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and ethyl acetate and dichloromethane were added to the residue. The mixture was filtered, washed with water and dried *in vacuo* to afford 4.98 g (59%) of (3-{4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyrylamino}propyl)carbamic acid tert-butyl ester.

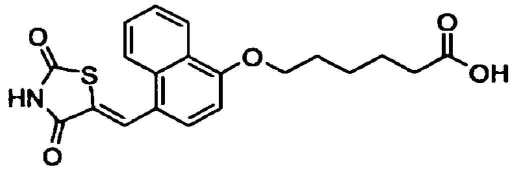
HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.79 min.

(3-{4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyrylamino}-propyl)carbamic acid tert-butyl ester (4.9 g, 9.5 mmol) was added dichloromethane (50 mL) and trifluoroacetic acid (50 mL) and the resulting mixture was stirred at room temperature for 45 minutes. The mixture was concentrated *in vacuo* and co-evaporated with toluene. To the residue was added ethyl acetate (100 mL) and the mixture was filtered and dried *in vacuo* to afford the title compound as the trifluoroacetic acid salt.

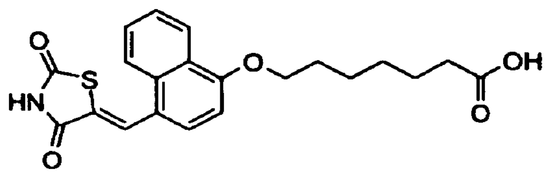
HPLC-MS (Method C): m/z: 414 (M+1); Rt = 2,27 min.

Compounds of the invention includes:

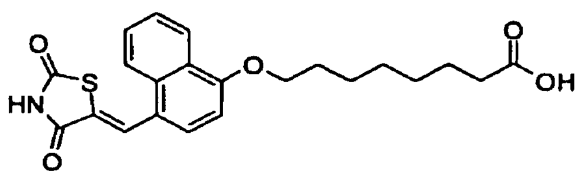
Example 322



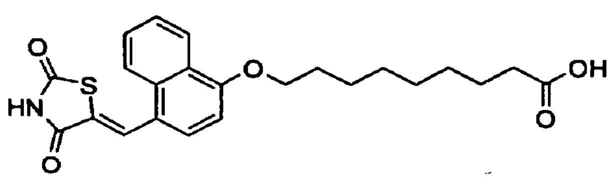
Example 323



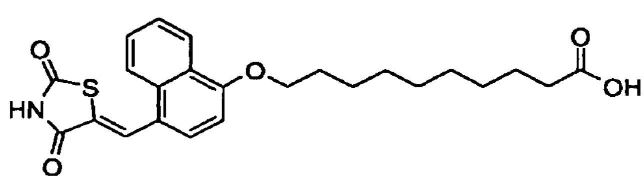
Example 324



Example 325

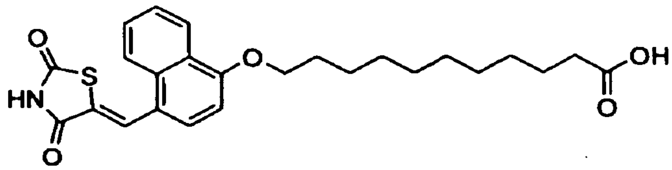


Example 326

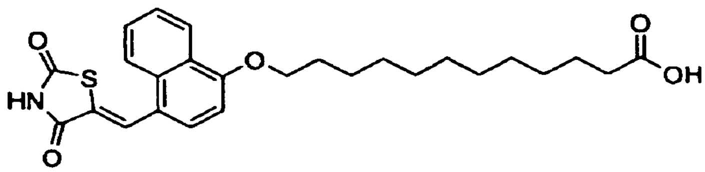


Example 327

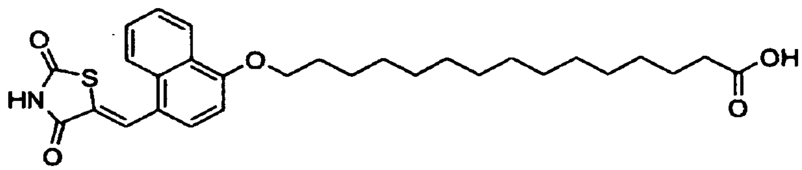
157



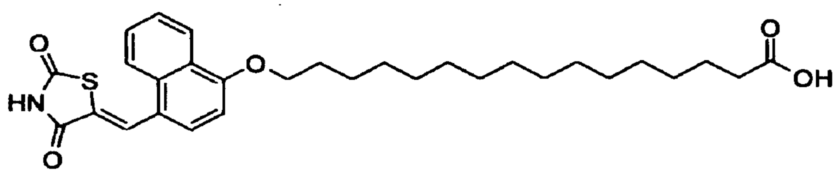
Example 328



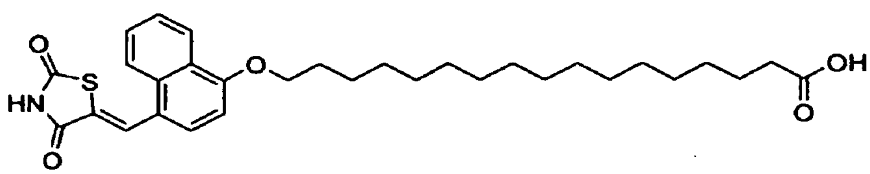
Example 329



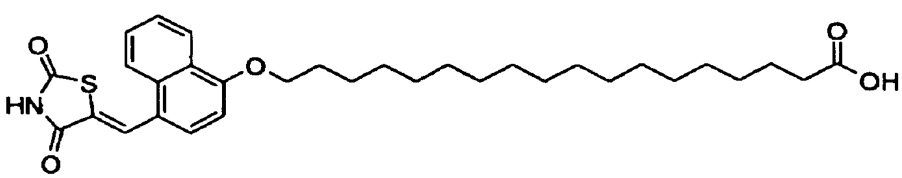
Example 330



Example 331

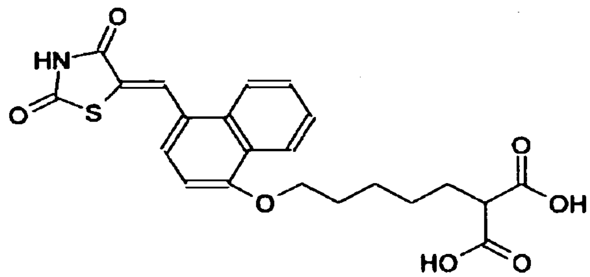


Example 332



Example 333 (Prepared analogously to General Procedure (D))

2-{5-[4-(2,4-Thiazolidindion-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid



A solution of 4-hydroxy-1-naphtaldehyde (1.0 g, 5.81 mmol), 2-(5-bromopentyl)malonic acid diethyl ester (2.07 g, 6.68 mmol) and potassium carbonate (4.01 g, 29 mmol) in DMF (50 mL) was stirred at 100° C for 3 hours. The mixture was cooled and the salt was filtered off. The solvent was then removed under reduced pressure to afford 2.9 g of crude 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid diethyl ester which was used for the next reaction without further purification.

HPLC-MS (Method C): m/z: 401 (M+1); Rt = 5.16 min. ^{1}H-NMR (DMSO-*d6*): δ = 1.18 (t, 6 H), 1,39 (m, 2 H), 1.55 (m, 2 H), 1.87 (m, 4 H), 3.48 (t, 1 H), 4.13 (m, 4 H), 4.27 (t, 2 H), 7.17 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.13 (d, 1 H), 8.29 (d, 1 H), 9.24 (d, 1 H), 10.19 (s, 1 H).

1.4 g (3.5 mmol) of crude 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid diethyl ester was treated with aqueous sodium hydroxide (1N, 8.75 mL, 8.75 mmol) and methanol (50 mL). The solution was stirred at 70° C for 5 hours and the mixture was concentrated under reduced pressure. Hydrochloric acid (6 N) was added until pH <2. The resulting slurry was stirred untill it solidified. The crystals were filtered off, washed with water and then dried *in vacuo* to afford 1.1 g (92%) of 2-[5-(4-formylnaphtalen-1-yloxy)pentyl]malonic acid. The product was used in the next step without further purification.

HPLC-MS (Method C): m/z: 345 (M+1); Rt = 3.52 min. ^{1}H-NMR(DMSO-*d6*): δ = 1,40 (m, 2 H), 1.55 (m, 2 H), 1.80 (m, 2 H), 1.90 (m, 2 H), 3.24 (t, 1 H), 4.29 (t, 2 H), 7.19 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.14 (d, 1 H), 8.30 (d, 1 H), 9.23 (d, 1 H), 10.18 (s, 1 H), 12.69 (s, 2 H).

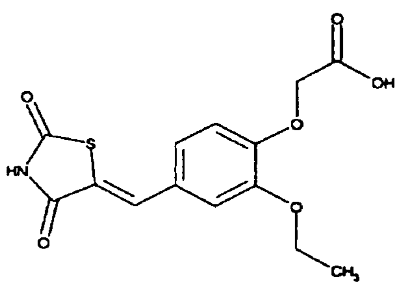
To a solution of 2-[5-(4-formylnaphtalen-1-yloxy) pentyl]malonic acid (0.36 g, 1.05 mmol) in acetic acid (10 mL) was added 2,4-thiazolidindione (0.16 g,1.36 mmol) and piperidine (0.52

mL, 5.25 mmol). The solution was heated to 105 °C for 24 hours. After cooling to room temperature, the solvents were removed *in vacuo*. Water was added to the residue. The precipitate was filtered off and washed with water. Recrystalisation from acetonitrile afforded 200 mg (43%) of the title compound as a solid.

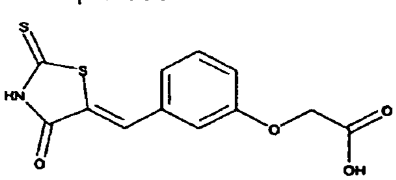
HPLC-MS (Method C): m/z: 422 ($M-CO_2+Na$); Rt = 4.08 min. ^1H-NMR(DMSO-d_6): δ = 1,41 (m, 2 H), 1.55 (m, 4 H), 1.88 (m, 2 H), 2.23 (t, 1 H), 4.24 (t, 2 H), 7.61-7.74 (m, 3 H), 8.12 (d, 1 H), 8.28 (d, 1 H), 8.38 (s, 1 H), 12.00 (s, 1 H), 12.59 (s, 2 H).

The following compounds are commercially available and may be prepared according to general procedure (D):

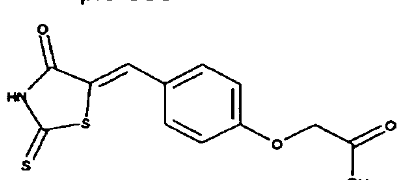
Example 334



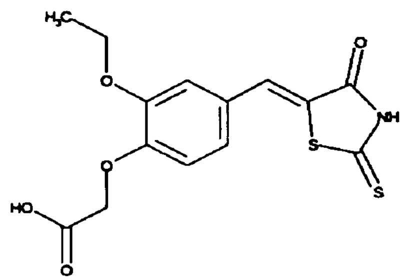
Example 335



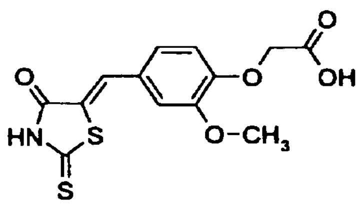
Example 336



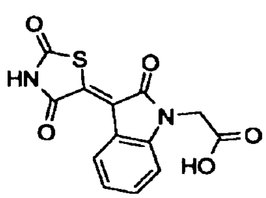
Example 337



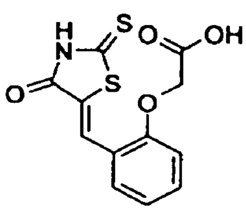
Example 338



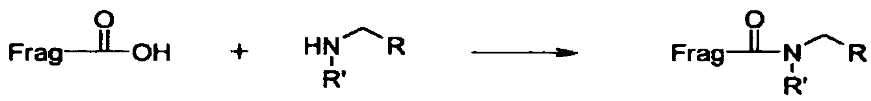
Example 339



Example 340



General procedure (N) for solution phase preparation of amides of general formula I_{13}:



I_{13}

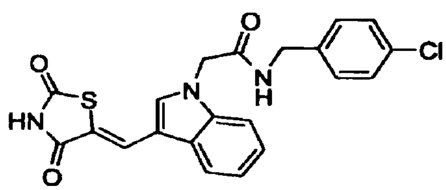
wherein Frag is any fragment carrying a carboxylic acid group, **R** is hydrogen, optionally substituted aryl or C_{1-8}-alkyl and **R'** is hydrogen or C_{1-4}-alkyl.

Frag-CO_2H may be prepared eg by general procedure (D) or by other similar procedures described herein, or may be commercially available.

The procedure is further illustrated in the following example 341:

Example 341 **(General procedure (N))**

N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1*H*-indol-1-yl]acetamide

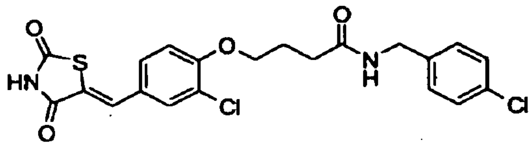


[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid (example 310, 90.7 mg, 0.3 mmol) was dissolved in NMP (1 mL) and added to a mixture of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide, hydrochloride (86.4 mg, 0.45 mmol) and 1-hydroxybenzotriazol (68.8 mg, 0.45 mmol) in NMP (1 mL). The resulting mixture was shaken at RT for 2 h. 4-Chlorobenzylamine (51 mg, 0.36 mmol) and DIPEA (46.4 mg, 0.36 mmol) in NMP (1 mL) were added to the mixture and the resulting mixture shaken at RT for 2 days. Subsequently ethyl acetate (10 mL) was added and the resulting mixture washed with 2x10 mL water followed by saturated ammonium chloride (5 mL). The organic phase was evaporated to dryness giving 75 mg (57%) of the title compound.

HPLC-MS (Method C): m/z: 426 (M+1); Rt. = 3.79 min.

Example 342 **(General procedure (N))**

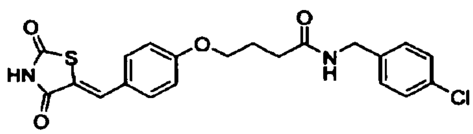
N-(4-Chlorobenzyl)-4-[2-chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 465 (M+1); Rt = 4.35 min.

Example 343 **(General procedure (N))**

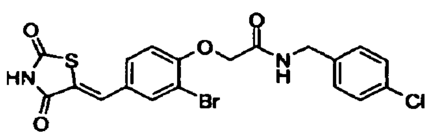
N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.68 min.

Example 344 **(General procedure (N))**

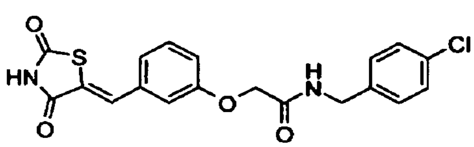
2-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]-*N*-(4-chlorobenzyl)acetamide



HPLC-MS (Method A): m/z: 483 (M+1); Rt = 4.06 min.

Example 345 **(General procedure (N))**

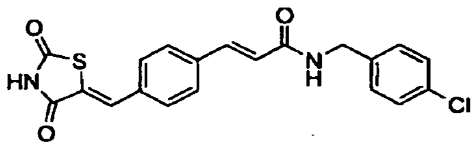
N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetamide



HPLC-MS (Method A): m/z: 403 (M+1); Rt = 4.03 min.

Example 346 **(General procedure (N))**

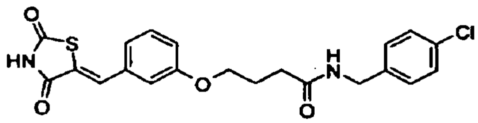
N-(4-Chlorobenzyl)-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]acrylamide



HPLC-MS (Method A): m/z: 399 (M+1); Rt = 3.82.

Example 347 **(General procedure (N))**

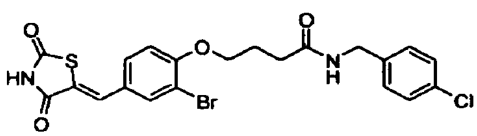
N-(4-Chlorobenzyl)-4-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide



HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.84 min.

Example 348 **(General procedure (N))**

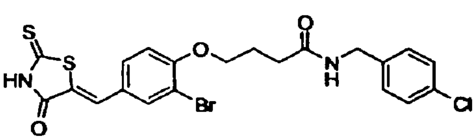
4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]-*N*-(4-chlorobenzyl)butyramide



HPLC-MS (Method A): m/z: 511 (M+1); Rt = 4.05 min.

Example 349 **(General procedure (N))**

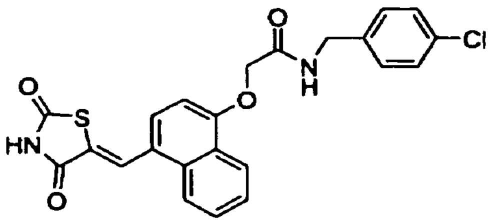
4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)-phenoxy]-*N*-(4-chlorobenzyl)-butyramide



HPLC-MS (Method A): m/z: 527 (M+1); Rt = 4.77 min.

Example 350 **(General procedure (N))**

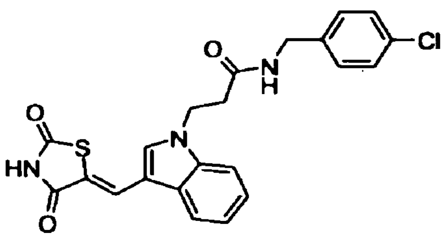
N-(4-Chlorobenzyl)-2-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetamide



HPLC-MS (Method C): m/z: 431 (M+1); Rt. = 4.03 min.

Example 351 **(General procedure (N))**

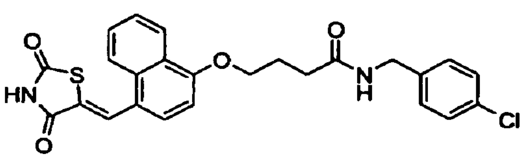
N-(4-Chlorobenzyl)-3-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1*H*-indol-1-yl]propionamide



HPLC-MS (Method C): m/z: 440 (M+1); Rt. = 3.57 min.

Example 352 **(General procedure (N))**

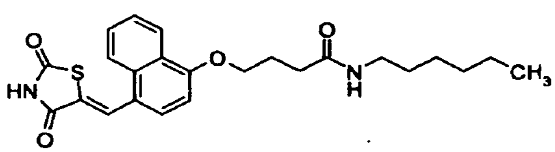
N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyramide



HPLC-MS (Method C): m/z: 481 (M+1); Rt = 4.08 min.

Example 353 **(General procedure (N))**

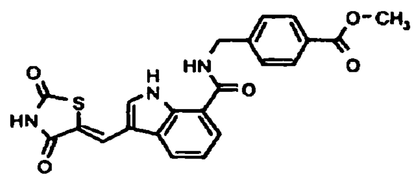
4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-*N*-hexylbutyramide



HPLC-MS (Method C): m/z: 441 (M+1); Rt = 4.31 min.

Example 354 (General Procedure (N))

4-({[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carbonyl]amino}methyl)benzoic acid methyl ester

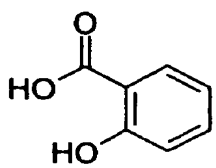


HPLC-MS (Method C): m/z: 436 (M+1); Rt.= 3.55 min.

The following salicylic acid derivatives do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

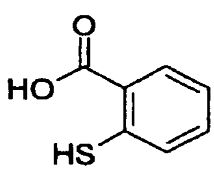
Example 355

Salicylic acid



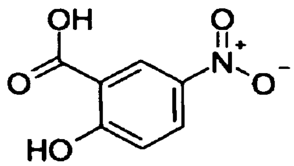
Example 356

Thiosalicylic acid (or: 2-Mercaptobenzoic acid)



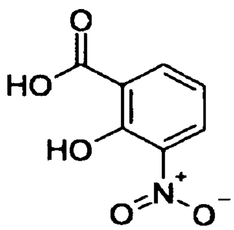
Example 357

2-Hydroxy-5-nitrobenzoic acid



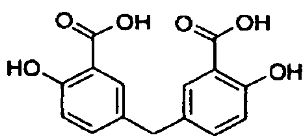
Example 358

3-Nitrosalicyclic acid



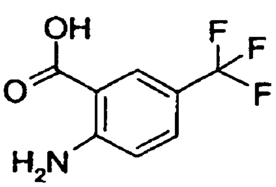
Example 359

5,5'-Methylenedisalicylic acid



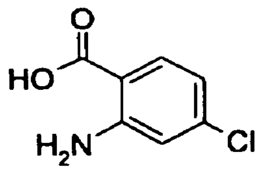
Example 360

2-Amino-5-trifluoromethylbenzoesyre



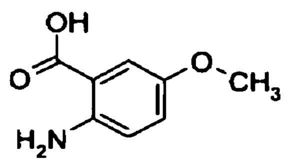
Example 361

2-Amino-4-chlorobenzoic acid

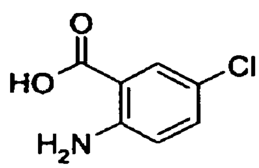


Example 362

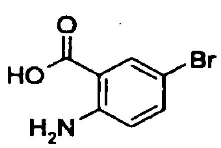
2-Amino-5-methoxybenzoesyre



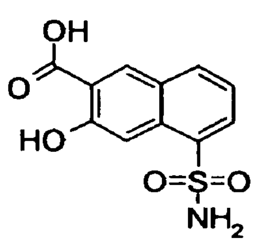
Example 363



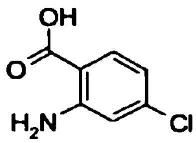
Example 364



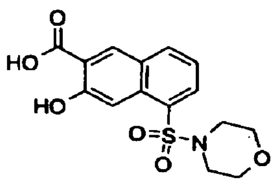
Example 365



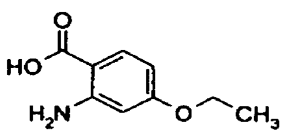
Example 366



Example 367

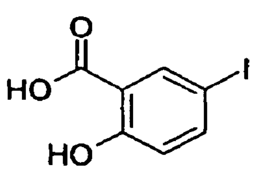


Example 368



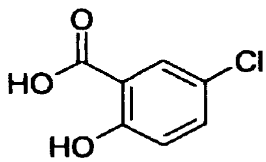
Example 369

5-Iodosalicylic acid



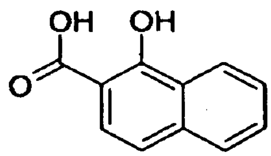
Example 370

5-Chlorosalicylic acid



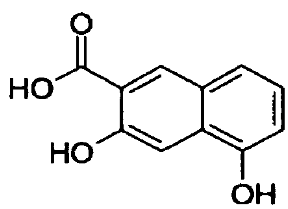
Example 371

1-Hydroxy-2-naphthoic acid



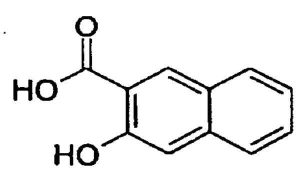
Example 372

3,5-Dihydroxy-2-naphthoic acid



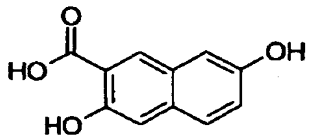
Example 373

3-Hydroxy-2-naphthoic acid



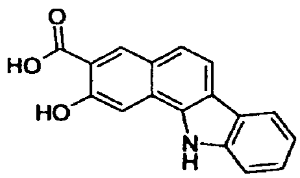
Example 374

3,7-Dihydroxy-2-naphthoic acid



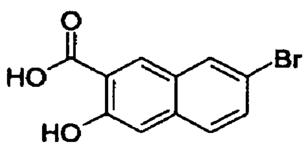
Example 375

2-Hydroxybenzo[a]carbazole-3-carboxylic acid



Example 376

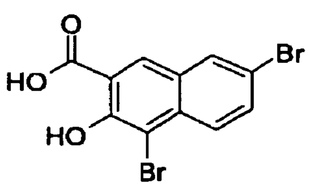
7-Bromo-3-hydroxy-2-naphthoic acid



This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8. HPLC-MS (Method A): m/z: 267 (M+1); Rt: = 3.78 min.

Example 377

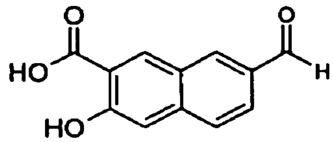
1,6-Dibromo-2-hydroxynaphthalene-3-carboxylic acid



This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8. HPLC-MS (Method A): m/z: 346 (M+1); Rt: = 4,19 min.

Example 378

7-Formyl-3-hydroxynaphthalene-2-carboxylic Acid

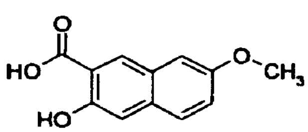


A solution of 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (15.0 g, 56.2 mmol) (example 376) in tetrahydrofuran (100 mL) was added to a solution of lithium hydride (893 mg, 112 mmol) in tetrahydrofuran (350 mL). After 30 minutes stirring at room temperature, the resulting solution was heated to 50 °C for 2 minutes and then allowed to cool to ambient temperature over a period of 30 minutes. The mixture was cooled to -78 °C, and butyllithium (1.6 M in hexanes, 53 mL, 85 mmol) was added over a period of 15 minutes. *N,N*-Dimethylformamide (8.7 mL, 8.2 g, 112 mmol) was added after 90 minutes additional stirring. The cooling was discontinued, and the reaction mixture was stirred at room temperature for 17 hours before it was poured into 1 N hydrochloric acid (aq.) (750 mL). The organic solvents were evaporated in vacuo, and the resulting precipitate was filtered off and rinsed with water (3 x 100 mL) to yield the crude product (16.2 g). Purification on silica gel (dichloromethane / methanol / acetic acid = 90:9:1) furnished the title compound as a solid.

^{1}H-NMR (DMSO-d_6): δ 11.95 (1H, bs), 10.02 (1H, s), 8.61 (1H, s), 8.54 (1H, s), 7.80 (2H, bs), 7.24 (1H, s); HPLC-MS (Method (A)): m/z: 217 (M+1); Rt = 2.49 min.

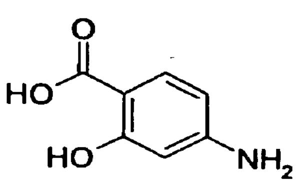
Example 379

3-Hydroxy-7-methoxy-2-naphthoic acid



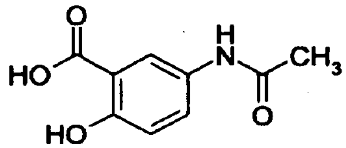
Example 380

4-Amino-2-hydroxybenzoic acid



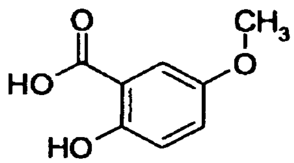
Example 381

5-Acetylamino-2-hydroxybenzoic acid



Example 382

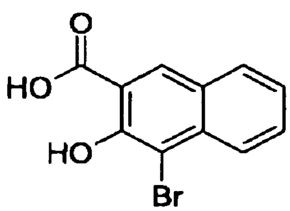
2-Hydroxy-5-methoxybenzoic acid



The following compounds were prepared as described below:

Example 383

4-Bromo-3-hydroxynaphthalene-2-carboxylic acid

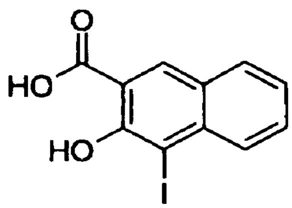


3-Hydroxynaphthalene-2-carboxylic acid (3.0 g, 15.9 mmol) was suspended in acetic acid (40 mL) and with vigorous stirring a solution of bromine (817 µL, 15.9 mmol) in acetic acid (10 mL) was added drop wise during 30 minutes. The suspension was stirred at room temperature for 1 hour, filtered and washed with water. Drying in vacuo afforded 3.74 g (88%) of 4-bromo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 7.49 (1H, t), 7.75 (1H, t), 8.07 (2H, "t"), 8.64 (1H, s). The substitution pattern was confirmed by a COSY experiment, showing connectivities between the 3 (4 hydrogen) "triplets". HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3.73 min.

Example 384

3-Hydroxy-4-iodonaphthalene-2-carboxylic acid



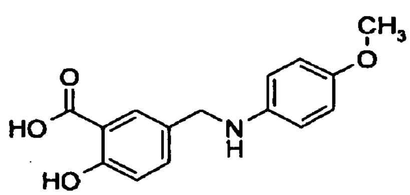
3-Hydroxynaphthalene-2-carboxylic acid (0.5 g, 2.7 mmol) was suspended in acetic acid (5 mL) and with stirring iodine monochloride (135 μL, 2.7 mml) was added. The suspension was stirred at room temperature for 1 hour, filtered and washed with water. Drying afforded 0.72 g (85%) of 4-iodo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

^{1}H-NMR (DMSO-d_6): δ 7.47 (1H, t), 7.73 (1H, t), 7.98 (1H, d), 8.05 (1H, d), 8.66 (1H, s).

HPLC-MS (Method A): m/z: 315 (M+1); Rt = 3.94 min.

Example 385

2-Hydroxy-5-[(4-methoxyphenylamino)methyl]benzoic acid



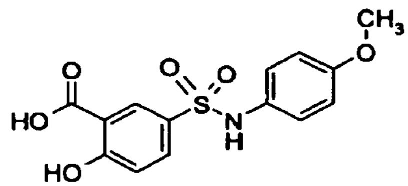
p-Anisidine (1.3 g, 10.6 mmol) was dissolved in methanol (20 mL) and 5-formylsalicylic acid (1.75 g, 10.6 mmol)was added and the resulting mixture was stirred at room temperature for 16 hours. The solid formed was isolated by filtration, re-dissolved in N-methyl pyrrolidone (20 mL) and methanol (2 mL). To the mixture was added sodium cyanoborohydride (1.2 g) and the mixture was heated to 70 °C for 3 hours. To the cooled mixture was added ethyl acetate (100 mL) and the mixture was extracted with water (100 mL) and saturated aqueous ammonium chloride (100 mL). The combined aqueous phases were concentrated *in vacuo* and a 2 g aliquot was purified by SepPac chromatography eluting with mixtures of aetonitrile and water containing 0.1% trifluoroacetic acid to afford the title compound.

HPLC-MS (Method A): m/z: 274 (M+1); Rt = 1.77 min.

^{1}H-NMR (methanol-d_4): δ 3.82 (3H, s), 4.45 (2H, s), 6.96 (1H, d), 7.03 (2H, d), 7.23 (2H, d), 7.45 (1H, dd), 7.92 (1H, d).

Example 386

2-Hydroxy-5-(4-methoxyphenylsulfamoyl)benzoic acid

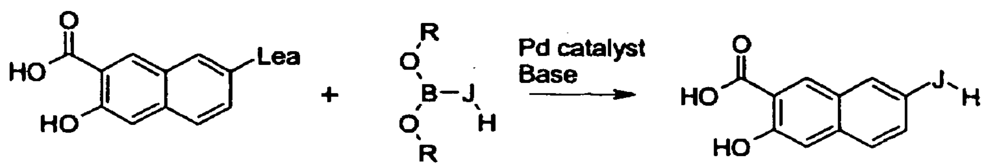


A solution of 5-chlrosulfonylsalicylic acid (0.96 g, 4.1 mmol) in dichloromethane (20 mL) and triethylamine (1.69 mL, 12.2 mmol) was added p-anisidine (0.49 g, 4.1 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The mixture was added dichloromethane (50 mL) and was washed with water (2 x 100 mL). Drying ($MgSO_4$) of the organic phase and concentration *in vacuo* afforded 0.57 g crude product. Purification by column chromatography on silica gel eluting first with ethyl acetate:heptane (1:1) then with methanol afforded 0.1 g of *the title compound.*

HPLC-MS (Method A): m/z: 346 (M+23); Rt = 2.89 min.

^{1}H-NMR (DMSO-d_6): δ 3.67 (3H, s), 6.62 (1H, d), 6.77 (2H, d), 6.96 (2H, d), 7.40 (1H, dd), 8.05 (1H, d), 9.6 (1H, bs).

General procedure (E) for preparation of compounds of general formula I_4:



I_4

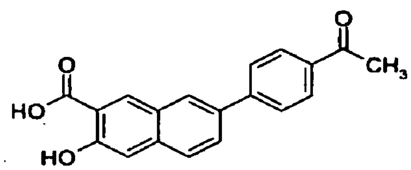
wherein Lea is a leaving group such as Cl, Br, I or OSO_2CF_3, R is hydrogen or C_1-C_6-alkyl, optionally the two R-groups may together form a 5-8 membered ring, a cyclic boronic acid ester, and J is as defined above.

An analogous chemical transformation has previously been described in the literature (Bumagin et al., *Tetrahedron*, **1997**, *53*, 14437-14450). The reaction is generally known as the Suzuki coupling reaction and is generally performed by reacting an aryl halide or triflate with an arylboronic acid or a heteroarylboronic acid in the presence of a palladium catalyst and a base such as sodium acetate, sodium carbonate or sodium hydroxide. The solvent can be water, acetone, DMF, NMP, HMPA, methanol, ethanol toluene or a mixture of two or more of these solvents. The reaction is performed at room temperature or at elevated temperature.

The general procedure (E) is further illustrated in the following example:

Example 387 **(General Procedure (E))**

7-(4-Acetylphenyl)-3-hydroxynaphthalene-2-carboxylic Acid



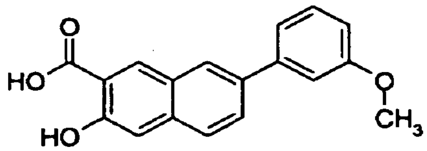
To 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (100 mg, 0.37 mmol) (example 376) was added a solution of 4-acetylphenylboronic acid (92 mg, 0.56 mmol) in acetone (2.2 mL) followed by a solution of sodium carbonate (198 mg, 1.87 mmol) in water (3.3 mL). A suspension of palladium(II) acetate (4 mg, 0.02 mmol) in acetone (0.5 mL) was filtered and added to the above solution. The mixture was purged with N_2 and stirred vigorously for 24 hours at room temperature. The reaction mixture was poured into 1 N hydrochloric acid (aq.) (60 mL) and the precipitate was filtered off and rinsed with water (3 x 40 mL). The crude product was dissolved in acetone (25 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration furnished the title compound as a solid (92 mg).

^{1}H-NMR (DMSO-d_6): δ 12.60 (1H, bs), 8.64 (1H, s), 8.42 (1H, s), 8.08 (2H, d), 7.97 (2H, d), 7.92 (2H, m), 7.33 (1H, s), 2.63 (3H, s); HPLC-MS (Method (A): m/z: 307 (M+1); Rt = 3.84 min.

The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. ethanol or by chromatography.

Example 388 **(General Procedure (E))**

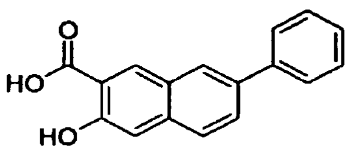
3-Hydroxy-7-(3-methoxyphenyl)naphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.60 min.

Example 389 **(General Procedure (E))**

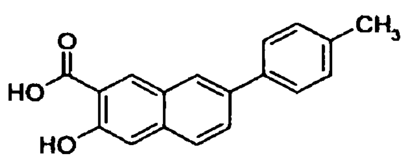
3-Hydroxy-7-phenylnaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 265 (M+1); Rt = 4.6 min.

Example 390 ***(General Procedure (E))***

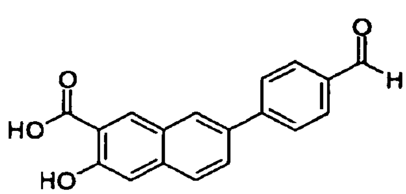
3-Hydroxy-7-p-tolylnaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 279 (M+1); Rt = 4.95 min.

Example 391 **(General Procedure (E))**

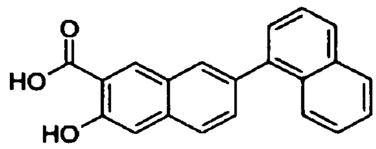
7-(4-Formylphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 293 (M+1); Rt = 4.4 min.

Example 392 **(General Procedure (E))**

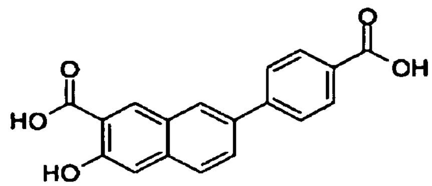
6-Hydroxy-[1,2]binaphthalenyl-7-carboxylic acid



HPLC-MS (Method (A)): m/z: 315 (M+1); Rt = 5.17 min.

Example 393 **(General Procedure (E))**

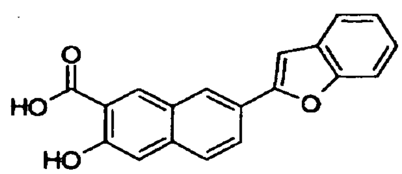
7-(4-Carboxy-phenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 3.60 min.

Example 394 **(General Procedure (E))**

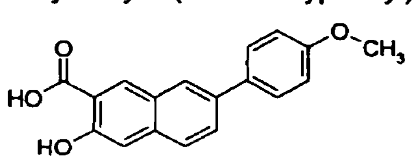
7-Benzofuran-2-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 305 (M+1); Rt = 4.97 min.

Example 395 **(General Procedure (E))**

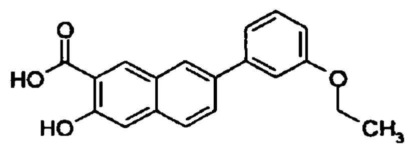
3-Hydroxy-7-(4-methoxyphenyl)-naphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.68 min.

Example 396 **(General Procedure (E))**

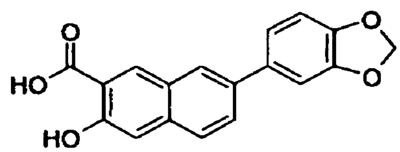
7-(3-Ethoxyphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 4.89 min.

Example 397 **(General Procedure (E))**

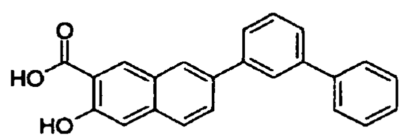
7-Benzo[1,3]dioxol-5-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 5.61 min.

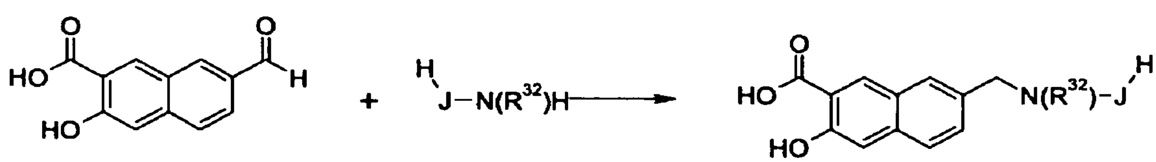
Example 398 **(General Procedure (E))**

7-Biphenyl-3-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 341 (M+1); Rt = 5.45 min.

General procedure (F) for preparation of compounds of general formula I_5:



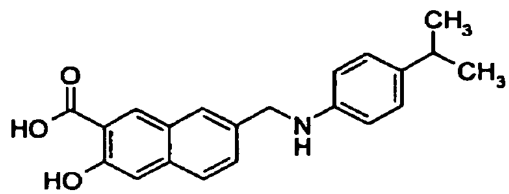
I_5

wherein R^{30} is hydrogen or C_1-C_6-alkyl and T is as defined above

This general procedure (F) is further illustrated in the following example:

Example 399 (General procedure (F))

3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



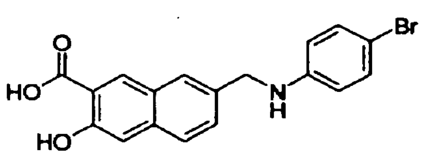
7-Formyl-3-hydroxynaphthalene-2-carboxylic acid (40 mg, 0.19 mmol) (example 378) was suspended in methanol (300 µL). Acetic acid (16 µL, 17 mg, 0.28 mmol) and 4-(2-propyl)aniline (40 µL, 40 mg, 0.30 mmol) were added consecutively, and the resulting mixture was stirred vigorously at room temperature for 2 hours. Sodium cyanoborohydride (1.0 M in tetrahydrofuran, 300 µL, 0.3 mmol) was added, and the stirring was continued for another 17 hours. The reaction mixture was poured into 6 N hydrochloric acid (aq.) (6 mL), and the precipitate was filtered off and rinsed with water (3 x 2 mL) to yield the title compound (40 mg) as its hydrochloride salt. No further purification was necessary.

^{1}H-NMR (DMSO-d_6): δ 10.95 (1H, bs), 8.45 (1H, s), 7.96 (1H, s), 7.78 (1H, d), 7.62 (1H, d), 7.32 (1H, s), 7.13 (2H, bd), 6.98 (2H, bd), 4.48 (2H, s), 2.79 (1H, sept), 1.14 (6H, d); HPLC-MS (Method (A)): m/z: 336 (M+1); Rt = 3.92 min.

The compounds in the following examples were made using this general procedure (F).

Example 400 **(General procedure (F))**

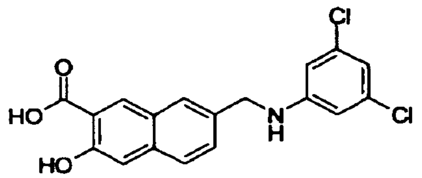
7-{[(4-Bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 372 (M+1); Rt = 4.31min.

Example 401 **(General procedure (F))**

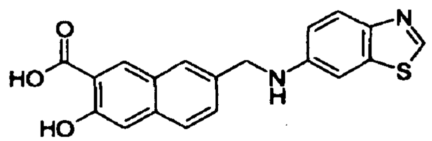
7-{[(3,5-Dichlorophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 362 (M+1); Rt = 4.75 min.

Example 402 **(General procedure (F))**

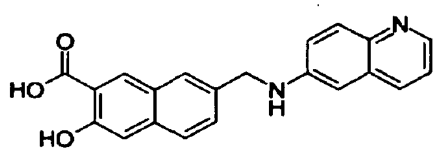
7-{[(Benzothiazol-6-yl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.43 min.

Example 403 **(General procedure (F))**

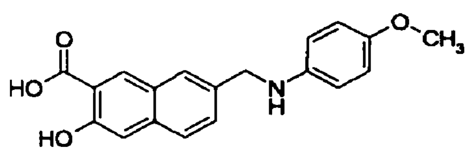
3-Hydroxy-7-{[(quinolin-6-yl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 345 (M+1); Rt = 2.26 min.

Example 404 **(General procedure (F))**

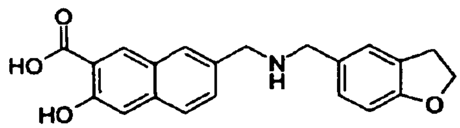
3-Hydroxy-7-{[(4-methoxyphenyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 324 (M+1); Rt = 2.57min.

Example 405 **(General procedure (F))**

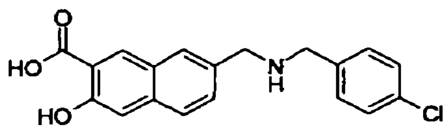
7-{[(2,3-Dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 350 (M+1); Rt = 2.22 min.

Example 406 **(General procedure (F))**

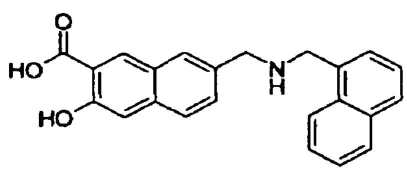
7-{[(4-Chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 2.45 min.

Example 407 **(General procedure (F))**

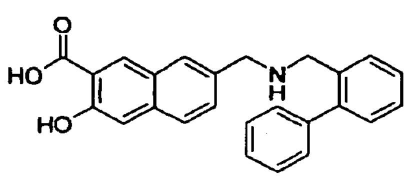
3-Hydroxy-7-{[(naphthalen-1-ylmethyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 357 (M+1); Rt = 2.63 min.

Example 408 **(General procedure (F))**

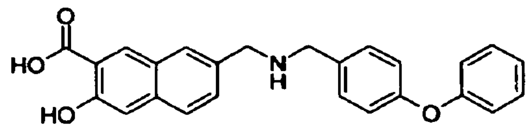
7-{[(Biphenyl-2-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 384 (M+1); Rt = 2.90 min.

Example 409 **(General procedure (F))**

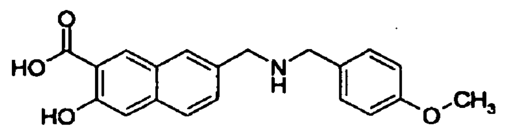
3-Hydroxy-7-{[(4-phenoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 400 (M+1); Rt = 3.15 min.

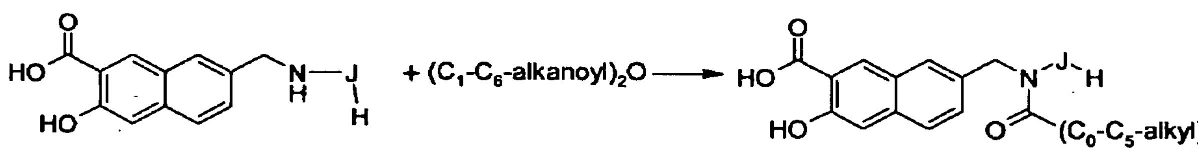
Example 410 **(General procedure (F))**

3-Hydroxy-7-{[(4-methoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 338 (M+1); Rt = 2.32 min.

General procedure (G) for preparation of compounds of general formula I_8:



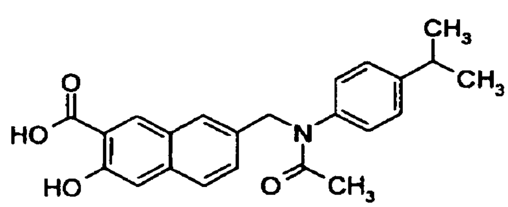
I_8

wherein J is as defined above and the moiety (C_1-C_6-alkanoyl)$_2$O is an anhydride.

The general procedure (G) is illustrated by the following example:

Example 411 (General procedure (G))

N-Acetyl-3-hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



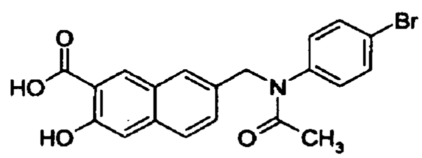
3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic acid (25 mg, 0.07 mmol) (example 399) was suspended in tetrahydrofuran (200 µL). A solution of sodium hydrogencarbonate (23 mg, 0.27 mmol) in water (200 µL) was added followed by acetic anhydride (14 µL, 15 mg, 0.15 mmol). The reaction mixture was stirred vigorously for 65 hours at room temperature before 6 N hydrochloric acid (4 mL) was added. The precipitate was filtered off and rinsed with water (3 x 1 mL) to yield the title compound (21 mg). No further purification was necessary.

^{1}H-NMR (DMSO-d_6): δ 10.96 (1H, bs), 8.48 (1H, s), 7.73 (1H, s), 7.72 (1H, d), 7.41 (1H, dd), 7.28 (1H, s), 7.23 (2H, d), 7.18 (2H, d), 4.96 (2H, s), 2.85 (1H, sept), 1.86 (3H, s), 1.15 (6H, d); HPLC-MS (Method (A)): m/z: 378 (M+1); Rt = 3.90 min.

The compounds in the following examples were prepared in a similar fashion.

Example 412 **(General procedure (G))**

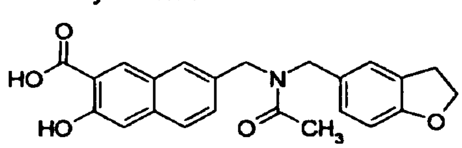
N-Acetyl-7-{[(4-bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 414 (M+1); Rt = 3.76 min.

Example 413 **(General procedure (G))**

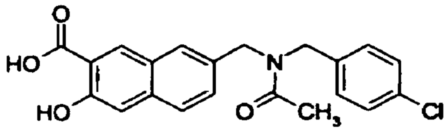
N-Acetyl-7-{[(2,3-dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 392 (M+1); Rt = 3.26 min.

Example 414 **(General procedure (G))**

N-Acetyl-7-{[(4-chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

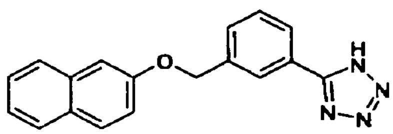


HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.67 min.

Compounds of the invention may also include tetrazoles:

Example 415

5-(3-(Naphthalen-2-yloxymethyl)-phenyl)-1*H*-tetrazole



To a mixture of 2-naphthol (10 g, 0.07 mol) and potassium carbonate (10 g, 0.073 mol) in acetone (150 mL), alpha-bromo-m-tolunitril (13.6 g, 0.07 mol) was added in portions. The reaction mixture was stirred at reflux temperature for 2.5 hours. The cooled reaction mixture was filtered and evaporated in vacuo affording an oily residue (19 g) which was dissolved in diethyl ether (150 mL) and stirred with a mixture of active carbon and $MgSO_4$ for 16 hours. The mixture was filtered and evaporated in vacuo affording crude 18.0 g (100 %) of 3-(naphthalen-2-yloxymethyl)-benzonitrile as a solid.

12 g of the above benzonitrile was recrystallised from ethanol (150 mL) affording 8.3 g (69 %) of 3-(naphthalen-2-yloxymethyl)-benzonitrile as a solid.

M.p. 60 - 61 °C.

Calculated for $C_{18}H_{13}NO$:

C, 83.37 %; H, 5.05 %; N, 5.40 %; Found

C, 83.51 %; H, 5.03 %; N, 5.38 %.

To a mixture of sodium azide (1.46 g, 22.5 mmol) and ammonium chloride (1.28 g, 24.0 mmol) in dry dimethylformamide (20 mL) under an atmosphere of nitrogen, 3-(naphthalen-2-yloxymethyl)-benzonitrile (3.9 g, 15 mmol) was added and the reaction mixture was stirred at 125 °C for 4 hours. The cooled reaction mixture was poured on to ice water (300 mL) and acidified to pH = 1 with 1 N hydrochloric acid. The precipitate was filtered off and washed with water, dried at 100 °C for 4 hours affording 4.2 g (93 %) of the title compound.

M.p. 200 - 202 °C.

Calculated for $C_{18}H_{14}N_4O$:

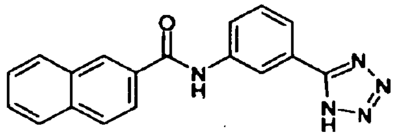
C, 71.51 %; H, 4.67 %; N, 18.54 %; Found

C, 72.11 %; H, 4.65 %; N, 17.43 %.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 5.36 (s, 2H), 7.29 (dd, 1H), 7.36 (dt, 1H), 7.47 (m, 2H), 7.66 (t, 1H), 7.74 (d, 1H), 7.84 (m, 3H), 8.02 (d, 1H), 8.22 (s, 1H).

Example 416

N-(3-(Tetrazol-5-yl)phenyl)-2-naphtoic acid amide



2-Naphtoic acid (10 g, 58 mmol) was dissolved in dichloromethane (100 mL) and N,N-dimethylformamide (0.2 mL) was added followed by thionyl chloride (5.1 ml, 70 mmol). The mixture was heated at reflux temperature for 2 hours. After cooling to room temperature, the mixture was added dropwise to a mixture of 3-aminobenzonitril (6.90 g, 58 mmol) and triethyl amine (10 mL) in dichloromethane (75 mL). The resulting mixture was stirred at room temperature for 30 minutes. Water (50 mL) was added and the volatiles was exaporated in vacuo. The resulting mixture was filtered and the filter cake was washed with water followed by heptane (2 x 25 mL). Drying in vacuo at 50 °C for 16 hours afforded 15.0 g (95 %) of N-(3-cyanophenyl)-2-naphtoic acid amide.

M.p. 138-140 °C

The above naphthoic acid amide (10 g, 37 mmol) was dissolved in N,N-dimethylformamide (200 mL) and sodium azide (2.63 g, 40 mmol) and ammonium chloride (2.16 g, 40 mmol) were added and the mixture heated at 125 °C for 6 hours. Sodium azide (1.2 g) and ammonium chloride (0.98 g) were added and the mixture heated at 125 °C for 16 hours. After cooling, the mixture was poured into water (1.5 l) and stirred at room temperature for 30 minutes. The solid formed was filtered off, washed with water and dried in vacuo at 50 °C for

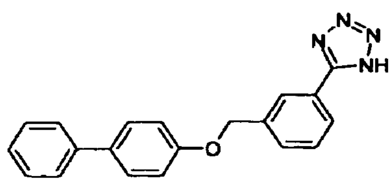
3 days affording 9.69 g (84 %) of the title compound as a solid which could be further purified by treatment with ethanol at reflux temperature.

^{1}H NMR (200 MHz, DMSO-d_6): δ_H 7.58-7.70 (m, 3H), 7.77 (d, 1H), 8.04-8.13 (m, 5H), 8.65 (d, 1H), 10.7 (s, 1H).

Calculated for $C_{18}H_{13}N_5O$, 0.75 H_2O:
C, 65.74 %; H, 4.44 %; N, 21.30 %. Found:
C, 65.58 %; H, 4.50 %; N, 21.05 %.

Example 417

5-[3-(Biphenyl-4-yloxymethyl)phenyl]-1*H*-tetrazole



To a solution of 4-phenylphenol (10.0 g, 59 mmol) in dry N,N-dimethyl-formamide (45 mL) kept under an atmosphere of nitrogen, sodium hydride (2.82 g, 71 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. A solution of m-cyanobenzyl bromide (13 g, 65 mmol) in dry N,N-dimethylformamide (45 mL) was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured on to ice water (150 mL). The precipitate was filtered of and washed with 50 % ethanol (3 x 50 mL), ethanol (2 x 50 mL), diethyl ether (80 mL), and dried in vacuo at 50 °C for 18 hours affording crude 17.39 g of 3-(biphenyl-4-yloxymethyl)-benzonitrile as a solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 5.14 (s, 2H), 7.05 (m, 2H), 7.30 - 7.78 (m, 11H).

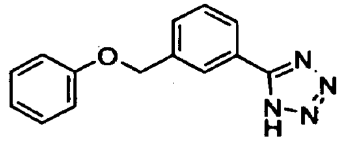
To a mixture of sodium azide (2.96 g, 45.6 mmol) and ammonium chloride (2.44 g, 45.6 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-yloxymethyl)-benzonitrile (10.0 g, 35.0 mmol) was added and the reaction mixture was stirred at 125 °C for 18 hours. The cooled reaction mixture was poured on to a mixture of 1N

hydrochloric acid (60 mL) and ice water (500 mL). The precipitate was filtered off and washed with water (3 x 100 mL), 50 % ethanol (3 x 100 mL), ethanol (50 mL), diethyl ether (50 mL), ethanol (80 mL), and dried in vacuo at 50 °C for 18 hours affording 8.02 g (70 %) of the title compound.

^{1}H NMR (200 MHz, DMSO-d_6) δ_H 5.31 (s, 2H), 7.19 (m, 2H), 7.34 (m, 1H), 7.47 (m, 2H), 7.69 (m, 6H), 8.05 (dt, 1H), 8.24 (s, 1H).

Example 418

5-(3-Phenoxymethyl)-phenyl)-tetrazole



3-Bromomethylbenzonitrile (5.00 g, 25.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), phenol (2.40 g, 25.5 mmol) and potassium carbonate (10.6 g, 77 mmol) were added. The mixture was stirred at room temperature for 16 hours. The mixture was poured into water (400 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated in vacuo to afford 5.19 g (97 %) 3-(phenoxymethyl)benzonitrile as an oil.

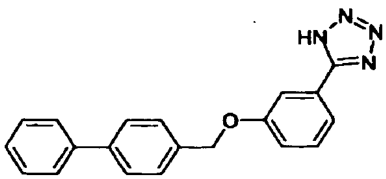
TLC: R_f = 0.38 (Ethyl acetate/heptane = 1:4)

The above benzonitrile (5.19 g, 24.8 mmol) was dissolved in N,N-dimethylformamide (100 mL) and sodium azide (1.93 g, 30 mmol) and ammonium chloride (1.59 g, 30 mmol) were added and the mixture was heated at 140 °C for 16 hours. After cooling, the mixture was poured into water (800 mL). The aqeous mixture was washed with ethyl acetate (200 mL). The pH of the aqueous phase was adjusted to 1 with 5 N hydrochloric acid and stirred at room temperature for 30 minutes. Filtration, washing with water and drying in vacuo at 50 °C afforded 2.06 g (33 %) of the title compound as a solid.

^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ_H 5.05 (s, 2H), 6.88 (m, 3H), 7.21 (m, 2H), 7.51 (m, 2H), 7.96 (dt, 1H), 8.14 (s, 1H).

Example 419

5-[3-(Biphenyl-4-ylmethoxy)phenyl]-1H-tetrazole



To a solution of 3-cyanophenol (5.0 g, 40.72 mmol) in dry N,N-dimethylformamide (100 mL) kept under an atmosphere of nitrogen, sodium hydride (2 g, 48.86 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. p-Phenylbenzyl chloride (9.26 g, 44.79 mmol) and potassium iodide (0.2 g, 1.21 mmol) were added and the reaction mixture was stirred at room temperature for 60 hours. The reaction mixture was poured on to a mixture of saturated sodium carbonate (100 mL) and ice water (300 mL). The precipitate was filtered of and washed with water (3 x 100 mL), n-hexane (2 x 80 mL) and dried in vacuo at 50 °C for 18 hours affording 11.34 g (98 %) of 3-(biphenyl-4-ylmethoxy)-benzonitrile as a solid.

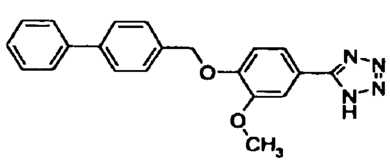
To a mixture of sodium azide (2.37 g, 36.45 mmol) and ammonium chloride (1.95 g, 36.45 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-ylmethoxy)-benzonitrile (8.0 g, 28.04 mmol) was added and the reaction mixture was stirred at

125 °C for 18 hours. To the cooled reaction mixture water (100 mL) was added and the reaction mixture stirred for 0.75 hour. The precipitate was filtered off and washed with water, 96 % ethanol (2 x 50 mL), and dried in vacuo at 50°C for 18 hours affording 5.13 g (56 %) of the title compound.

^{1}H NMR (200 MHz, DMSO-d_6) δ_H 5.29 (s, 2H), 7.31 (dd, 1H), 7.37 - 7.77 (m, 12H).

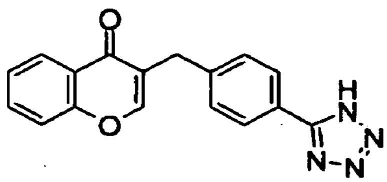
Example 420

5-[4-(Biphenyl-4-ylmethoxy)-3-methoxyphenyl]-1H-tetrazol



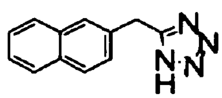
This compound was made similarly as described in example 419.

Example 421



Example 422

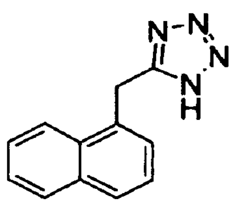
5-(2-Naphtylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 415, step 2.

Example 423

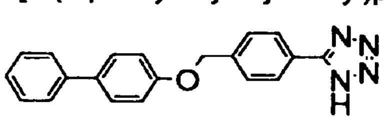
5-(1-Naphtylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 415, step 2.

Example 424

5-[4-(Biphenyl-4-yloxymethyl)phenyl]-1H-tetrazole



A solution of alpha-bromo-p-tolunitrile (5.00 g, 25.5 mmol), 4-phenylphenol (4.56 g, 26.8 mmol), and potassium carbonate (10.6 g, 76.5 mmol) in N,N-dimethylformamide (75 mL) was stirred vigorously for 16 hours at room temperature. Water (75 mL) was added and the

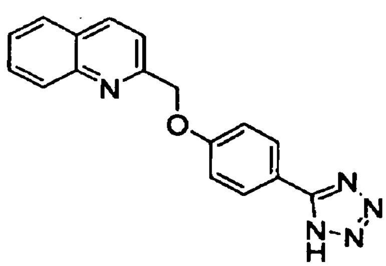
mixture was stirred at room temperature for 1 hour. The precipitate was filtered off and washed with thoroughly with water. Drying in vacuo over night at 50 °C afforded 7.09 g (97 %) of 4-(biphenyl-4-yloxymethyl)benzonitrile as a solid.

The above benzonitrile (3.00 g, 10.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), and sodium azide (1.03 g, 15.8 mmol) and ammonium chloride (0.84 g, 15.8 mmol) were added and the mixture was stirred 16 hours at 125 °C. The mixture was cooled to room temperature and water (50 mL) was added. The suspension was stirred overnight, filtered, washed with water and dried in vacuo at 50 °C for 3 days to give crude 3.07 g (89 %) of the title compound. From the mother liquor crystals were colected and washed with water, dried by suction to give 0.18 g
(5 %) of the title compound as a solid.

^{1}H NMR (200 MHz, DMSO-d_6): δ_H 5.21 (s, 2H), 7.12 (d, 2H), 7.30 (t, 1H), 7.42 (t, 2H), 7.56-7.63 (m, 6H), 8.03 (d, 2H).

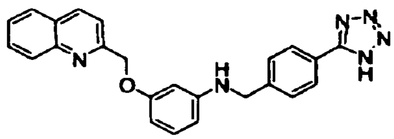
Calculated for $C_{20}H_{16}N_4O$, $2H_2O$:
C, 65.92 %; H, 5.53 %; N, 15.37 %. Found:
C, 65.65 %; H, 5.01 %; N, 14.92 %.

Example 425

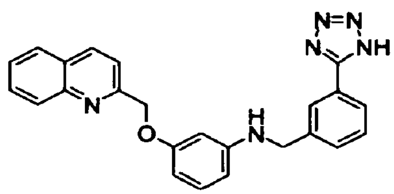


This compound was prepared similarly as described in example 419.

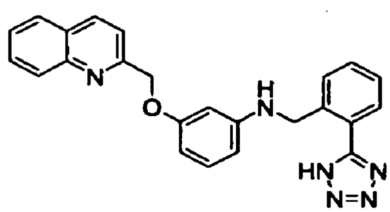
Example 426



Example 427

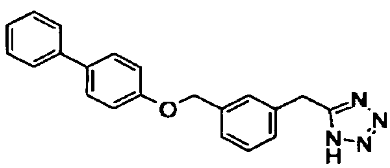


Example 428



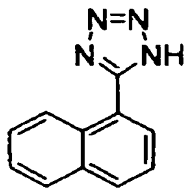
Example 429

5-(3-(Biphenyl-4-yloxymethyl)-benzyl)-1*H*-tetrazole



Example 430

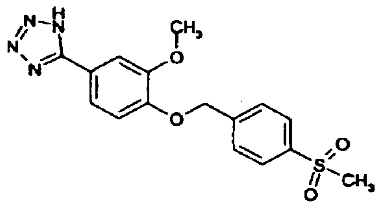
5-(1-Naphthyl)-1*H*-tetrazole



This compound was prepared similarly as described in example 415, step 2.

Example 431

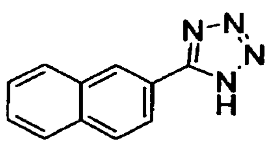
5-[3-Methoxy-4-(4-methylsulfonylbenzyloxy)phenyl]-1*H*-tetrazole



This compound was made similarly as described in example 419.

Example 432

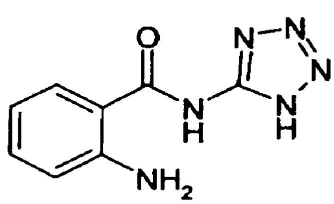
5-(2-Naphthyl)-1*H*-tetrazole



This compound was prepared similarly as described in example 415, step 2.

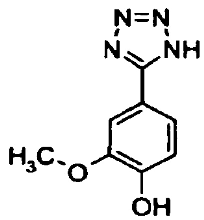
Example 433

2-Amino-N-(1*H*-tetrazol-5-yl)-benzamide



Example 434

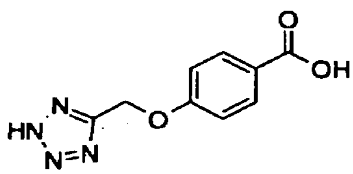
5-(4-Hydroxy-3-methoxyphenyl)-1*H*-tetrazole



This compound was prepared similarly as described in example 415, step 2.

Example 435

4-(2H-Tetrazol-5-ylmethoxy)benzoic acid



To a mixture of methyl 4-hydroxybenzoate (30.0 g, 0.20 mol), sodium iodide (30.0 g, 0.20 mol) and potassium carbonate (27.6 g, 0.20 mol) in acetone (2000 mL) was added chloroacetonitrile (14.9 g , 0.20 mol). The mixture was stirred at RT for 3 days. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone and chloroacetonitrile (6.04 g,0.08 mol), sodium iodide (12.0 g, 0.08 mol) and potassium carbonate (11.1 g, 0.08 mol) were added and the mixture was stirred for 16 hours at RT and at 60 °C. More chloroacetonitrile was added until the conversion was 97%. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford methyl 4-cyanomethyloxybenzoate in quantitative yield. This compound was used without further purification in the following step.

A mixture of methyl 4-cyanomethyloxybenzoate (53.5 g,0.20 mol), sodium azide (16.9 g, 0.26 mol) and ammonium chloride (13.9 g, 0.26 mol) in DMF 1000 (mL) was refluxed overnight under N_2. After cooling, the mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with ethyl acetate. The combined organic phases were washed

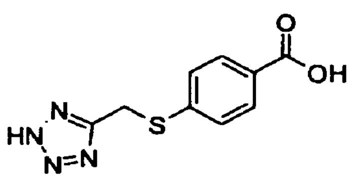
with brine, dried over Na_2SO_4 and concentrated *in vacuo*, to afford methyl 4-(2*H*-tetrazol-5-ylmethoxy)benzoate. This compound was used as such in the following step.

Methyl 4-(2H-Tetrazol-5-ylmethoxy)-benzoate was refluxed in 3N sodium hydroxide. The reaction was followed by TLC (DCM:MeOH = 9:1). The reaction mixture was cooled, acidified and the product filtered off. The impure product was washed with DCM, dissolved in MeOH, filtered and purified by column chromatography on silica gel (DCM:MeOH = 9:1).The resulting product was recrystallised from DCM:MeOH=95:5. This was repeated until the product was pure. This afforded 13.82 g (30 %) of the title compound.

^{1}H-NMR (DMSO-d_6): 4.70 (2H, s), 7.48 (2H, d), 7.73 (2H, d), 13 (1H, bs).

Example 436

4-(2H-Tetrazol-5-ylmethylsulfanyl)benzoic acid



To a solution of sodium hydroxide (10.4 g, 0.26 mol) in degassed water (600 mL) was added 4-mercaptobenzoic acid (20.0 g, 0.13 mol). This solution was stirred for 30 minutes. To a solution of potassium carbonate (9.0 g, 65 mmol) in degassed water (400 mL) was added chloroacetonitrile (9.8 g, (0.13 mol) portion-wise. These two solutions were mixed and stirred for 48 hours at RT under N_2. The mixture was filtered and washed with heptane. The aqueous phase was acidified with 3N hydrochloric acid and the product was filtered off, washed with water and dried, affording 4-cyanomethylsulfanylbenzoic acid (27.2 g, 88%). This compound was used without further purification in the following step.

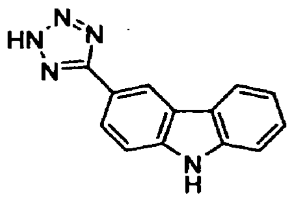
A mixture of 4-cyanomethylsulfanylbenzoic acid (27.2 g, 0.14 mol), sodium azide (11.8 g, 0,18 mol) and ammonium chloride (9.7 g, 0.18 mol) in DMF (1000 mL) was refluxed overnight under N_2. The mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Water was added and the precipitate was filtered off. The aqueous layer was concentrated *in vacuo*, water was added and the precipitate filtered off. The combined impure products were purified by column

chromatography using DCM:MeOH = 9:1 as eluent, affording the title compound (5.2 g, 16%).

^{1}H-NMR (DMSO-d_6): 5.58 (2H, s), 7.15 (2H, d), 7.93 (2H, d), 12.7 (1H, bs).

Example 437

3-(2*H*-Tetrazol-5-yl)-9*H*-carbazole



3-Bromo-9*H*-carbazole was prepared as described by Smith *et al.* in *Tetrahedron* **1992**, *48*, 7479-7488.
A solution of 3-bromo-9*H*-carbazole (23.08 g, 0.094 mol) and cuprous cyanide (9.33 g, 0.103 mol) in *N*-methyl-pyrrolidone (300 ml) was heated at 200 °C for 5 h. The cooled reaction mixture was poured on to water (600 ml) and the precipitate was filtered off and washed with ethyl acetate (3 x 50 ml). The filtrate was extracted with ethyl acetate (3 x 250 ml) and the combined ethyl acetate extracts were washed with water (150 ml), brine (150 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was crystallised from heptanes and recrystallised from acetonitrile (70 ml) affording 7.16 g (40 %) of 3-cyano-9*H*-carbazole as a solid. M.p. 180 - 181 °C.

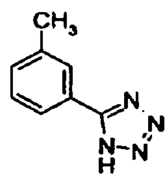
3-Cyano-9*H*-carbazole (5.77 g, 30 mmol) was dissolved in *N,N*-dimethylformamide (150 ml), and sodium azide (9.85 g, 152 mmol), ammonium chloride (8.04 g, 150 mmol) and lithium chloride (1.93 g, 46 mmol) were added and the mixture was stirred for 20 h at 125 °C. To the reaction mixture was added an additional portion of sodium azide (9.85 g, 152 mmol) and ammonium chloride (8.04 g, 150 mmol) and the reaction mixture was stirred for an additional 24 h at 125 °C. The cooled reaction mixture was poured on to water (500 ml). The suspension was stirred for 0.5 h, and the precipitate was filtered off and washed with water (3 x 200 ml) and dried *in vacuo* at 50 °C. The dried crude product was suspended in diethyl ether (500 ml) and stirred for 2 h, filtered off and washed with diethyl ether (2 x 200 ml) and dried *in vacuo* at 50 °C affording 5.79 g (82 %) of the title compound as a solid.

^{1}H-NMR (DMSO-d_6): δ 11.78 (1H, bs), 8.93 (1H, d), 8.23 (1H, d), 8.14 (1H, dd), 7.72 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.28 (1H, t); HPLC-MS (Method C): m/z: 236 (M+1); Rt = 2.77 min.

The following commercially available tetrazoles do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

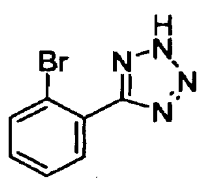
Example 438

5-(3-Tolyl)-1*H*-tetrazole



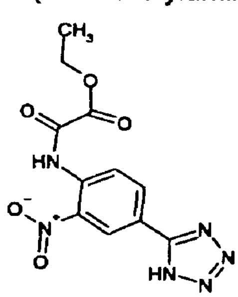
Example 439

5-(2-Bromophenyl)tetrazole

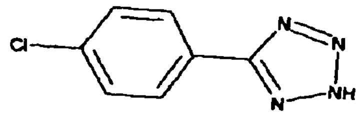


Example 440

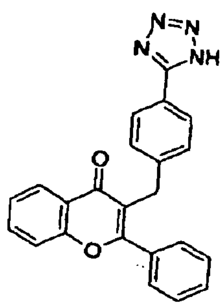
5-(4-Ethoxalylamino-3-nitrophenyl)tetrazole



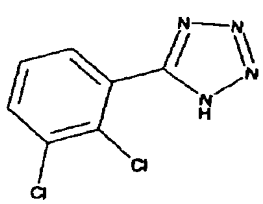
Example 441



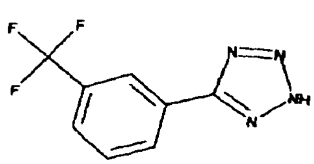
Example 442



Example 443

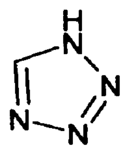


Example 444



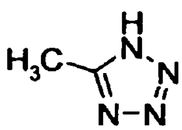
Example 445

Tetrazole



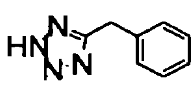
Example 446

5-Methyltetrazole



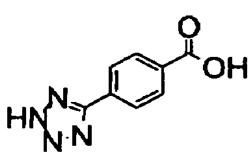
Example 447

5-Benzyl-2H-tetrazole



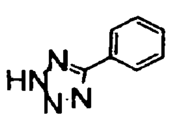
Example 448

4-(2H-Tetrazol-5-yl)benzoic acid



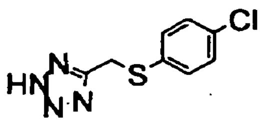
Example 449

5-Phenyl-2H-tetrazole



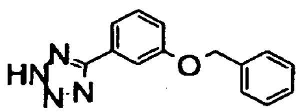
Example 450

5-(4-Chlorophenylsulfanylmethyl)-2H-tetrazole



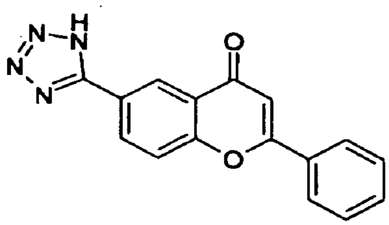
Example 451

5-(3-Benzyloxyphenyl)-2H-tetrazole

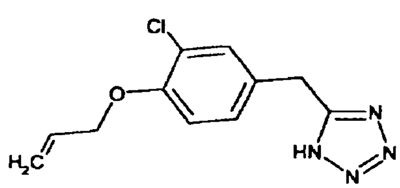


Example 452

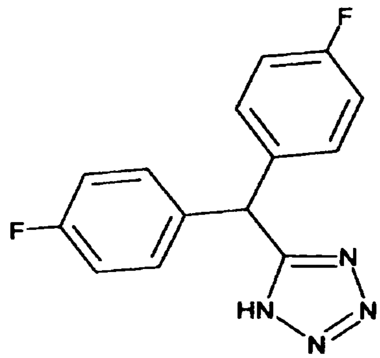
2-Phenyl-6-(1H-tetrazol-5-yl)-chromen-4-one



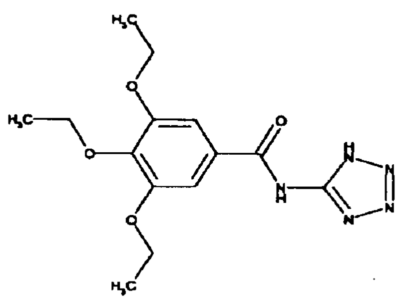
Example 453



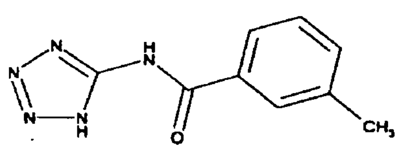
Example 454



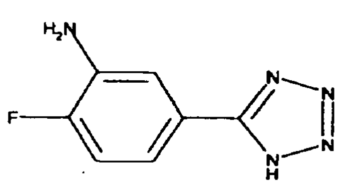
Example 455



Example 456

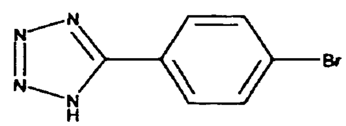


Example 457

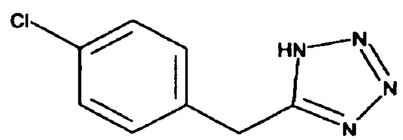


Example 458

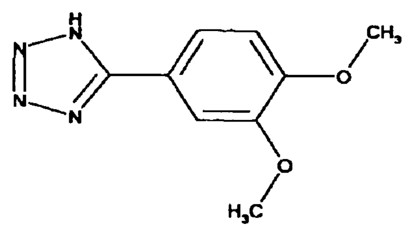
5-(4-Bromo-phenyl)-1H-tetrazole



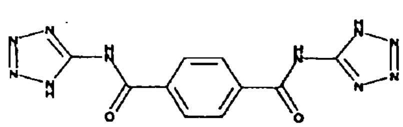
Example 459



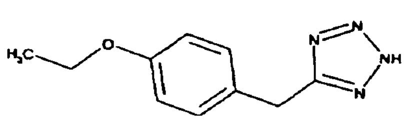
Example 460



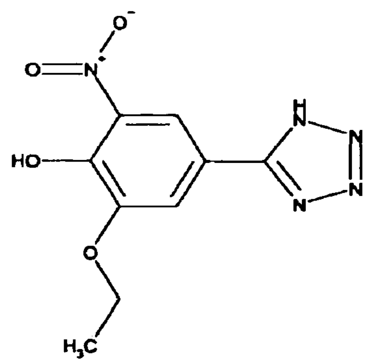
Example 461



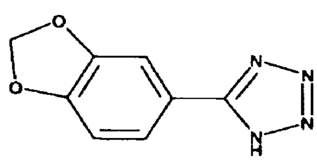
Example 462



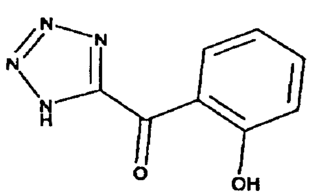
Example 463



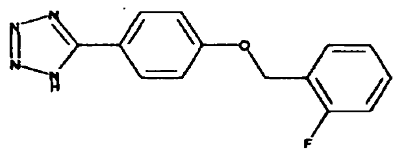
Example 464



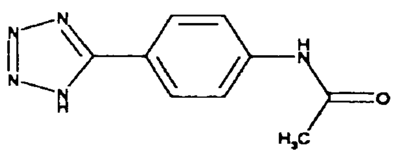
Example 465



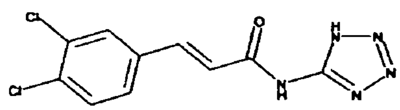
Example 466



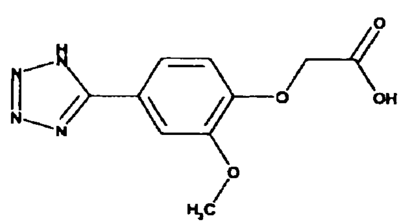
Example 467



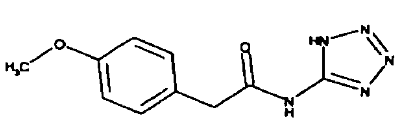
Example 468



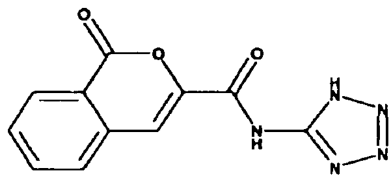
Example 469



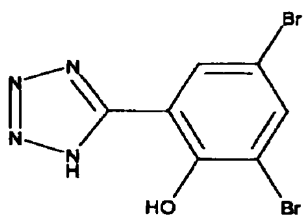
Example 470



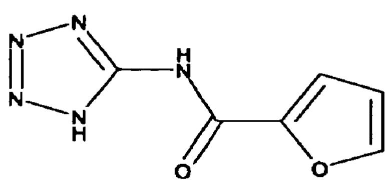
Example 471



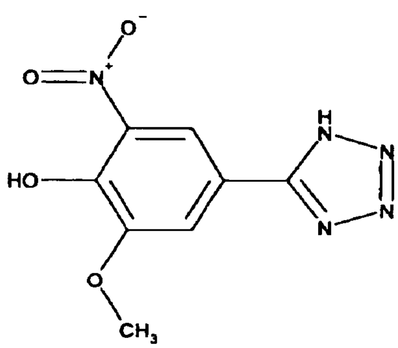
Example 472



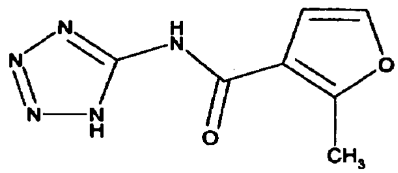
Example 473



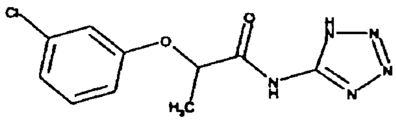
Example 474



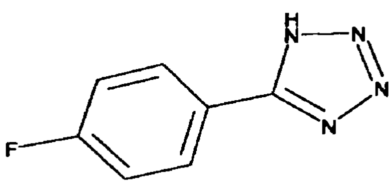
Example 475



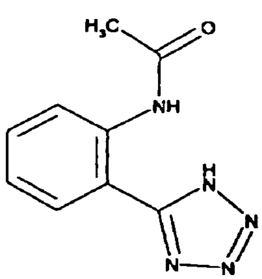
Example 476



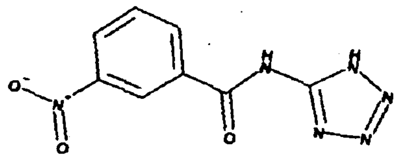
Example 477



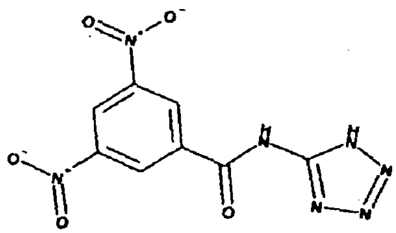
Example 478



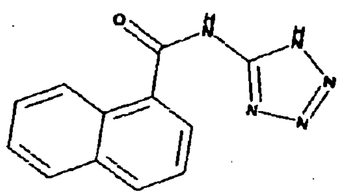
Example 479



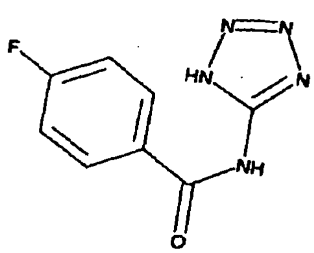
Example 480



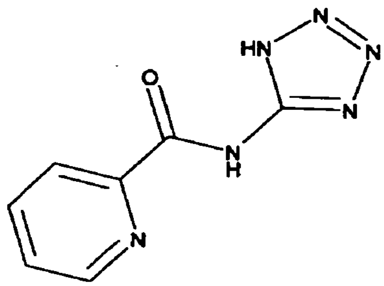
Example 481



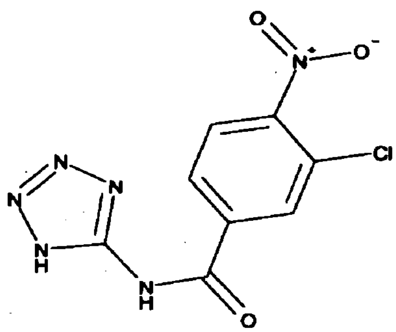
Example 482



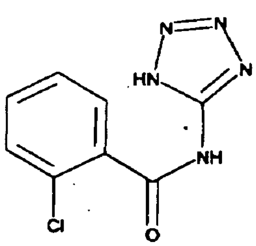
Example 483



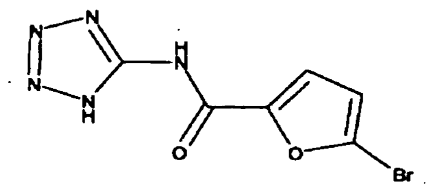
Example 484



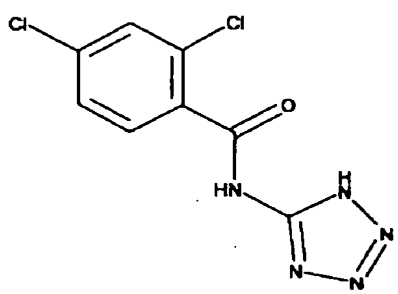
Example 485



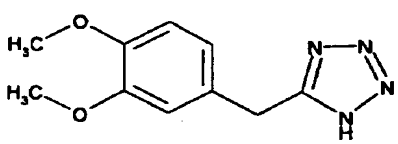
Example 486



Example 487

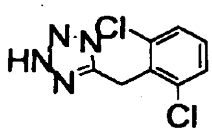


Example 488

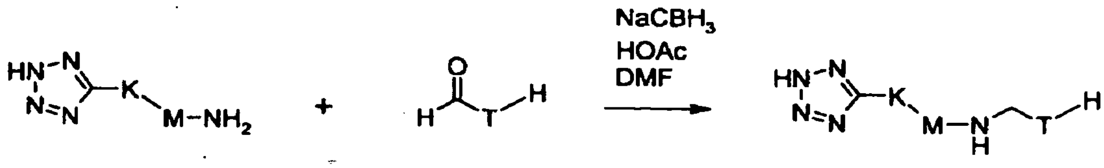


Example 489

5-(2,6-Dichlorobenzyl)-2*H*-tetrazole



General procedure (H) for preparation of compounds of general formula I_7:



I_7

wherein K, M, and T are as defined above.

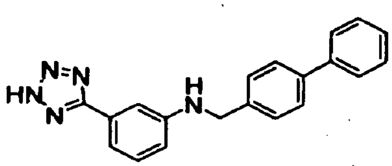
The reaction is generally known as a reductive alkylation reaction and is generally performed by stirring an aldehyde with an amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. As reducing agent sodium cyano borohydride or sodium triacetoxy borohydride may be used. The reaction is performed between 20°C and 120°C, preferably at room temperature.

When the reductive alkylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (H) is further illustrated in the following example 490:

Example 490 **(General procedure (H))**

Biphenyl-4-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



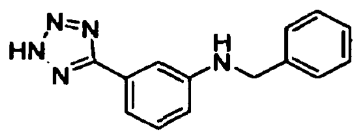
A solution of 5-(3-aminophenyl)-2*H*-tetrazole (example 706, 48 mg, 0.3 mmol) in DMF (250 µL) was mixed with a solution of 4-biphenylylcarbaldehyde (54 mg, 0.3 mmol) in DMF (250 µL) and acetic acid glacial (250 µL) was added to the mixture followed by a solution of sodium cyano borohydride (15 mg, 0.24 mmol) in methanol (250 µL). The resulting mixture was shaken at room temperature for 2 hours. Water (2 mL) was added to the mixture and the resulting mixture was shaken at room temperature for 16 hours. The mixture was centrifugated (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The

residue was washed with water (3 mL), centrifugated (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The residue was dried *in vacuo* at 40 °C for 16 hours to afford the title compound as a solid.

HPLC-MS (Method C): m/z: 328 (M+1), 350 (M+23); Rt = 4.09 min.

Example 491 **(General procedure (H))**

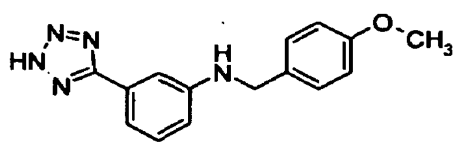
Benzyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,74 min.

Example 492 **(General procedure (H))**

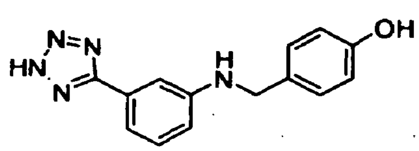
(4-Methoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 282,2 (M+1); Rt = 3,57min.

Example 493 **(General procedure (H))**

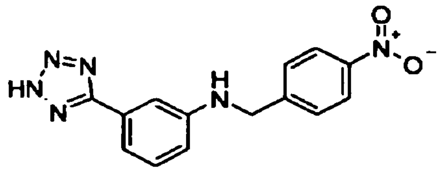
4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol



HPLC-MS (Method D): m/z: 268,4 (M+1); Rt = 2,64 min.

Example 494 **(General procedure (H))**

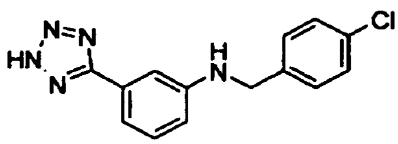
(4-Nitrobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 297,4 (M+1); Rt = 3,94 min.

Example 495 **(General procedure (H))**

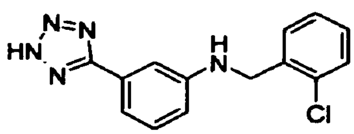
(4-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 287,2 (M+1); Rt = 4,30 min.

Example 496 **(General procedure (H))**

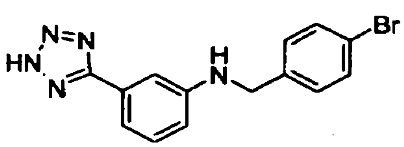
(2-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,40 min.

Example 497 **(General procedure (H))**

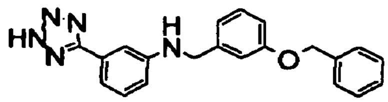
(4-Bromobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z:332 (M+1); Rt = 4,50 min.

Example 498 **(General procedure (H))**

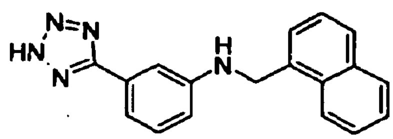
(3-Benzyloxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,94 min.

Example 499 **(General procedure (H))**

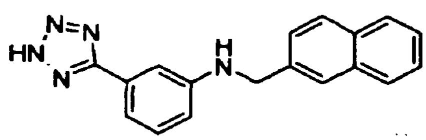
Naphthalen-1-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 500 **(General procedure (H))**

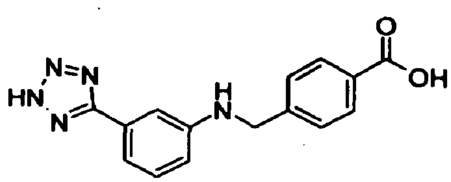
Naphthalen-2-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,60 min.

Example 501 **(General procedure (H))**

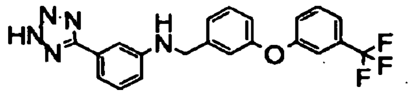
4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,24 min.

Example 502 **(General procedure (H))**

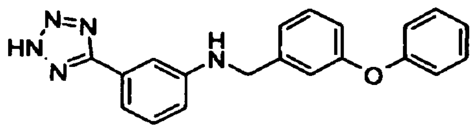
[3-(2*H*-Tetrazol-5-yl)-phenyl]-[3-(3-trifluoromethyl-phenoxy)benzyl]amine



HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

Example 503 **(General procedure (H))**

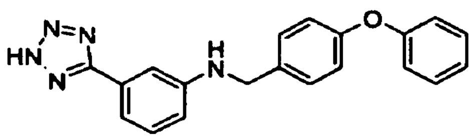
(3-Phenoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,04 min.

Example 504 **(General procedure (H))**

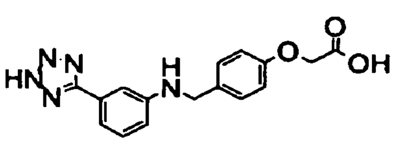
(4-Phenoxy-benzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,00 min.

Example 505 **(General procedure (H))**

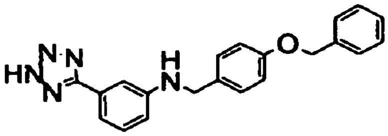
(4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenoxy)acetic acid



HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,10 min.

Example 506 **(General procedure (H))**

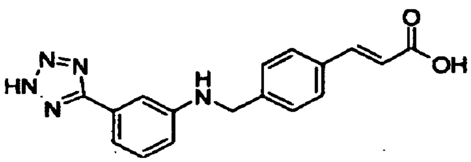
(4-Benzyloxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 507 **(General procedure (H))**

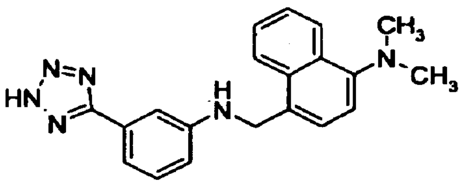
3-(4-{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenyl)acrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,60 min.

Example 508 **(General procedure (H))**

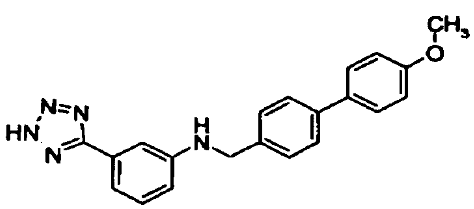
Dimethyl-(4-{[3-(2*H*-tetrazol-5-yl)phenylamino]methyl}naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,07 min.

Example 509 **(General procedure (H))**

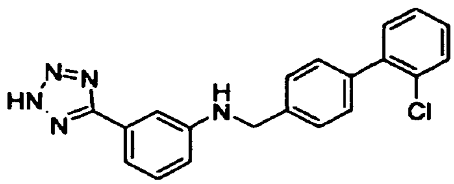
(4'-Methoxybiphenyl-4-ylmethyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 510 **(General procedure (H))**

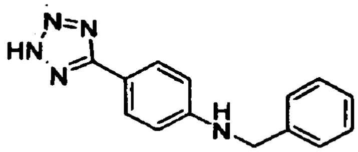
(2'-Chlorobiphenyl-4-ylmethyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,27 min.

Example 511 **(General procedure (H))**

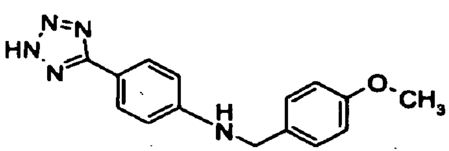
Benzyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



For preparation of starting material, see example 707.
HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,97 min.

Example 512 **(General procedure (H))**

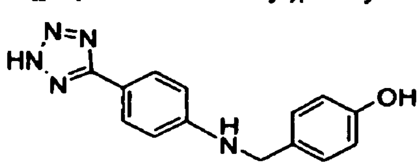
(4-Methoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 282 (M+1); Rt = 3,94 min.

Example 513 **(General procedure (H))**

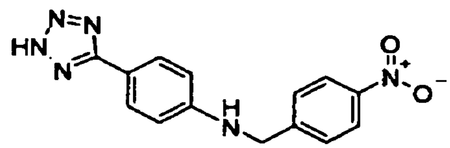
4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol



HPLC-MS (Method D): m/z: 268 (M+1); Rt = 3,14 min.

Example 514 **(General procedure (H))**

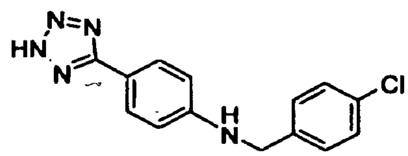
(4-Nitrobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: (M+1); Rt = 3,94 min.

Example 515 **(General procedure (H))**

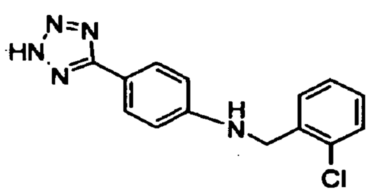
(4-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: (M+1); Rt = 4,47 min.

Example 516 **(General procedure (H))**

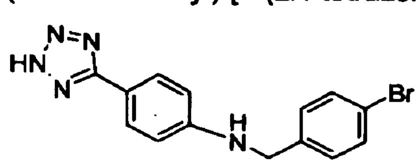
(2-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,37 min.

Example 517 **(General procedure (H))**

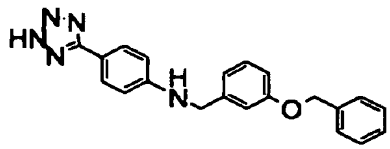
(4-Bromobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 331 (M+1); Rt = 4,57 min.

Example 518 **(General procedure (H))**

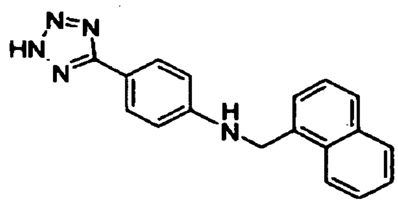
(3-Benzyloxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,07min.

Example 519 **(General procedure (H))**

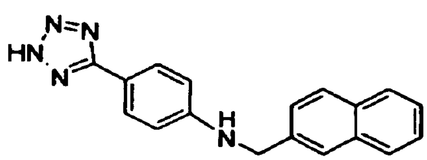
Naphthalen-1-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 520 **(General procedure (H))**

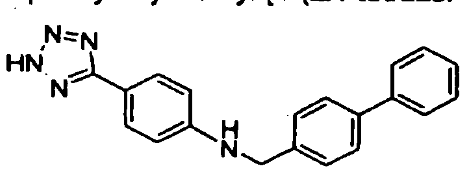
Naphthalen-2-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 521 **(General procedure (H))**

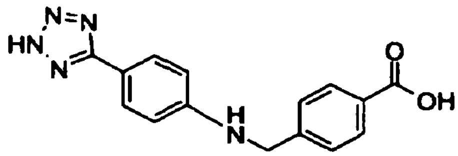
Biphenyl-4-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 328 (M+1); Rt = 5,07 min.

Example 522 **(General procedure (H))**

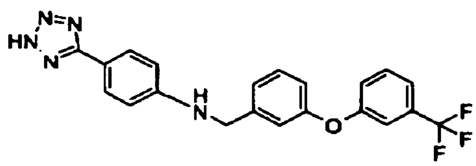
4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,34 min.

Example 523 **(General procedure (H))**

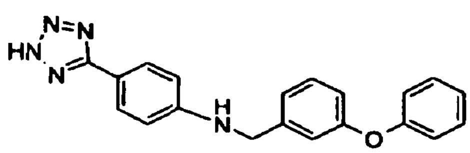
[4-(2*H*-Tetrazol-5-yl)phenyl]-[3-(3-trifluoromethylphenoxy)benzyl]amine



HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

Example 524 **(General procedure (H))**

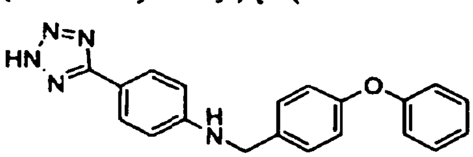
(3-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,07 min.

Example 525 **(General procedure (H))**

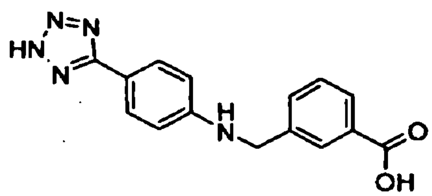
(4-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine



HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,03 min.

Example 526 **(General procedure (H))**

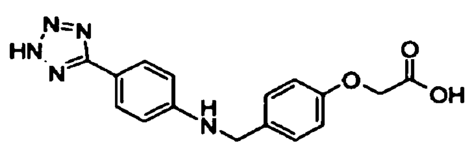
3-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 3,47 min.

Example 527 **(General procedure (H))**

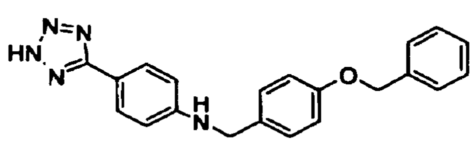
(4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenoxy)acetic acid



HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,40 min.

Example 528 **(General procedure (H))**

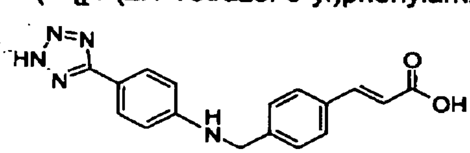
(4-Benzyloxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,14 min.

Example 529 **(General procedure (H))**

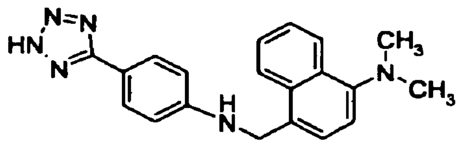
3-(4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenyl)acrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,66 min.

Example 530 **(General procedure (H))**

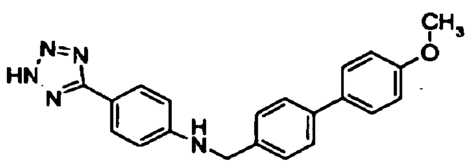
Dimethyl-(4-{[4-(2*H*-tetrazol-5-yl)phenylamino]methyl}naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,10 min.

Example 531 **(General procedure (H))**

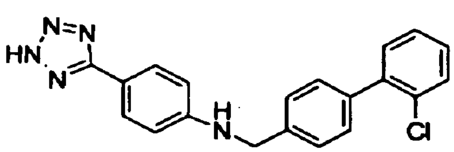
(4'-Methoxybiphenyl-4-ylmethyl)-[4-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,04 min.

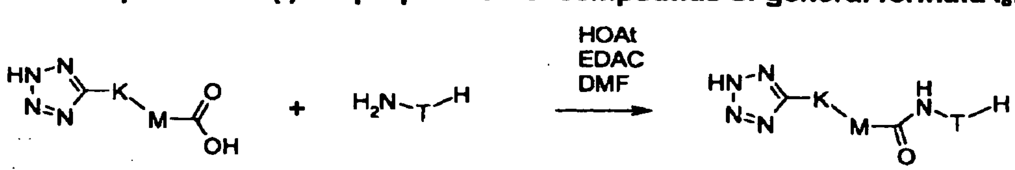
Example 532 **(General procedure (H))**

(2'-Chlorobiphenyl-4-ylmethyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine



HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,30 min.

General procedure (I) for preparation of compounds of general formula I_8:



I_8

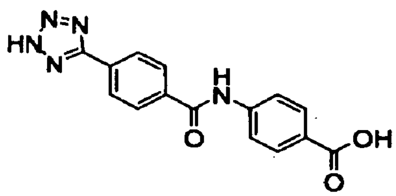
wherein K, M and T are as defined above.

This procedure is very similar to general procedure (A), the only difference being the carboxylic acid is containing a tetrazole moiety. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (I) is further illustrated in the following example 533:

Example 533 **(General procedure (I))**

4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]benzoic acid

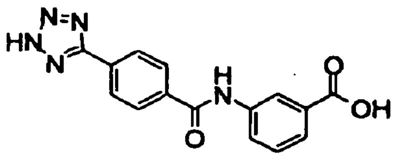


To a solution of 4-(2H-tetrazol-5-yl)benzoic acid (example 448, 4 mmol) and HOAt (4.2 mmol) in DMF (6 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.2 mmol) and the resulting mixture was stirred at room temperature for 1 hour. An alquot of this HOAt-ester solution (0.45 mL) was mixed with 0.25 mL of a solution of 4-aminobenzoic acid (1.2 mmol in 1 mL DMF). (Anilines as hydrochlorides can also be utilised, a slight excess of triethylamine was added to the hydrochloride suspension in DMF prior to mixing with the HOAt-ester.) The resulting mixture was shaken for 3 days at room temperature. 1N hydrochloric acid (2 mL) was added and the mixture was shaken for 16 hours at room temperature. The solid was isolated by centrifugation (alternatively by filtration or extraction) and was washed with water (3 mL). Drying *in vacuo* at 40 °C for 2 days afforded the title compound.

HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.83 min.

Example 534 **(General procedure (I))**

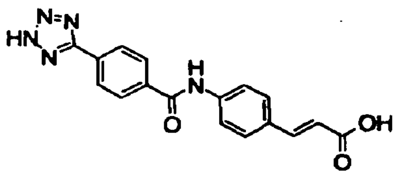
3-[4-(2*H*-Tetrazol-5-yl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.89 min.

Example 535 **(General procedure (I))**

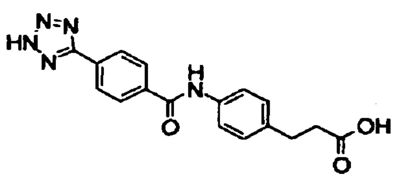
3-{4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 336 (M+1); Rt = 3.10 min.

Example 536 **(General procedure (I))**

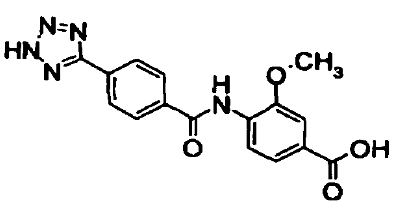
3-{4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 338 (M+1); Rt = 2.97 min.

Example 537 **(General procedure (I))**

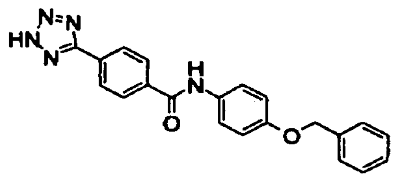
3-Methoxy-4-[4-(2*H*-tetrazol-5-yl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 340 (M+1); Rt = 3.03 min.

Example 538 **(General procedure (I))**

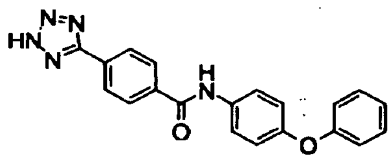
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 372 (M+1); Rt = 4.47 min.

Example 539 **(General procedure (I))**

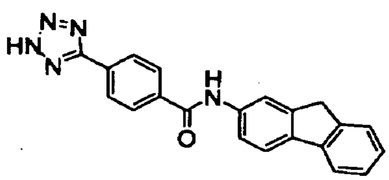
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4.50 min.

Example 540 **(General procedure (I))**

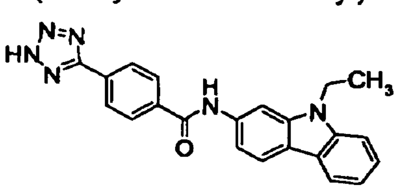
N-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 354 (M+1); Rt = 4.60 min.

Example 541 **(General procedure (I))**

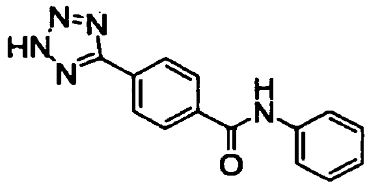
N-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 383 (M+1); Rt = 4.60 min.

Example 542 **(General procedure (I))**

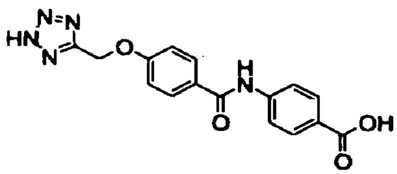
N-Phenyl-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 266 (M+1); Rt = 3.23 min.

Example 543 **(General procedure (I))**

4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid

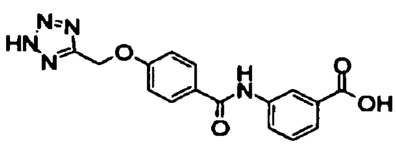


The starting material was prepared as described in example 435.

HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.83 min.

Example 544 **(General procedure (I))**

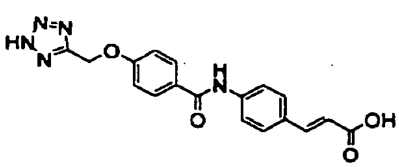
3-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.90 min.

Example 545 **(General procedure (I))**

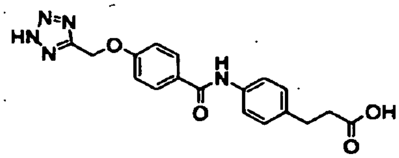
3-{4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 366 (M+1); Rt = 3.07 min.

Example 546 **(General procedure (I))**

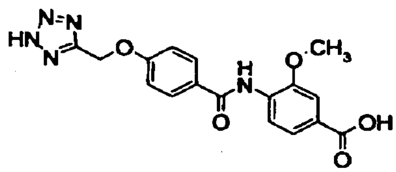
3-{4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 368 (M+1); Rt = 2.97 min.

Example 547 **(General procedure (I))**

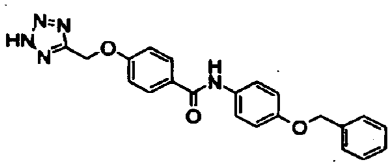
3-Methoxy-4-[4-(2*H*-tetrazol-5-ylmethoxy)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 370 (M+1); Rt = 3.07 min.

Example 548 **(General procedure (I))**

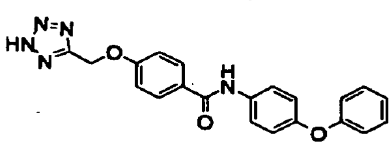
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 402 (M+1); Rt = 4.43 min.

Example 549 **(General procedure (I))**

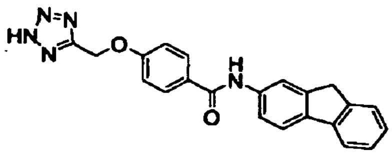
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 388 (M+1); Rt = 4.50 min.

Example 550 **(General procedure (I))**

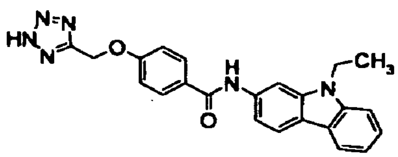
N-(9H-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 384 (M+1); Rt = 4.57 min.

Example 551 **(General procedure (I))**

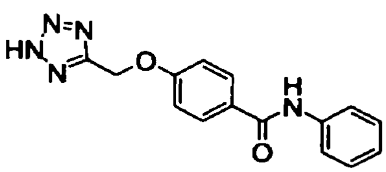
N-(9-Ethyl-9H-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 413 (M+1); Rt = 4.57 min.

Example 552 **(General procedure (I))**

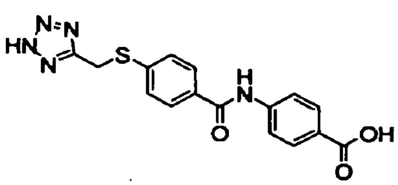
N-Phenyl-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3.23 min.

Example 553 **(General procedure (I))**

4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid

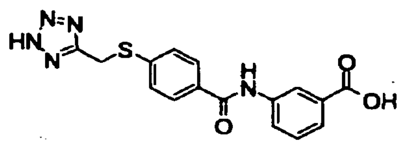


The starting material was prepared as described in example 436.

HPLC-MS (Method D): m/z: 356 (M+1); Rt = 2.93 min.

Example 554 **(General procedure (I))**

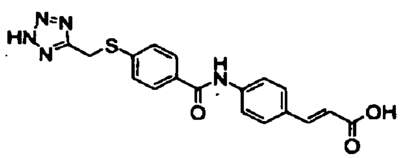
3-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 356 (M+1); Rt = 3.00 min.

Example 555 **(General procedure (I))**

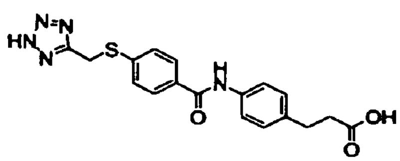
3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 382 (M+1); Rt = 3.26 min.

Example 556 **(General procedure (I))**

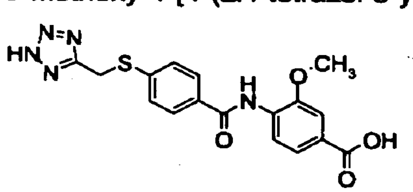
3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 384 (M+1); Rt = 3.10 min.

Example 557 **(General procedure (I))**

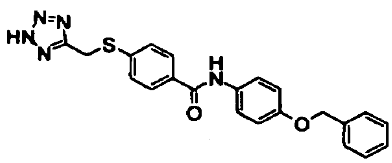
3-Methoxy-4-[4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 386 (M+1); Rt = 3.20 min.

Example 558 **(General procedure (I))**

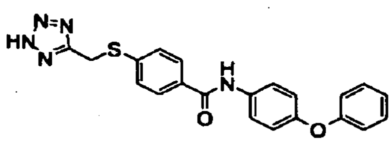
N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 418 (M+1); Rt = 4.57 min.

Example 559 **(General procedure (I))**

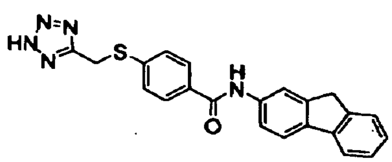
N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 404 (M+1); Rt = 4.60 min.

Example 560 **(General procedure (I))**

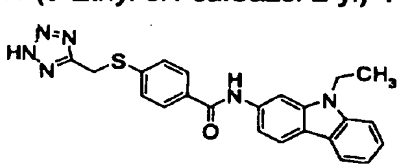
N-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 400 (M+1); Rt = 4.67 min.

Example 561 **(General procedure (I))**

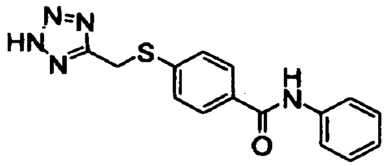
N-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 429 (M+1); Rt = 4.67 min.

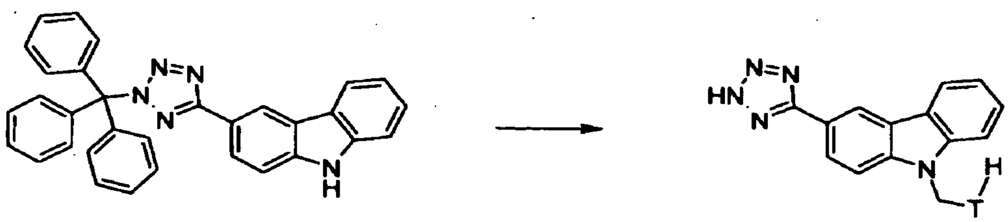
Example 562 **(General procedure (I))**

N-Phenyl-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 312 (M+1); Rt = 3.40 min.

General procedure (J) for solution phase preparation of amides of general formula I_9:



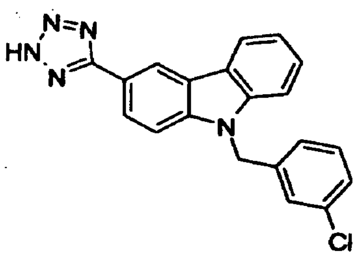
I_9

wherein T is as defined above.

This general procedure (J) is further illustrated in the following example.

Example 563 **(General procedure (J)).**

9-(3-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



3-(2*H*-Tetrazol-5-yl)-9*H*-carbazole (example 437, 17 g, 72.26 mmol) was dissolved in *N,N*-dimethylformamide (150 mL). Triphenylmethyl chloride (21.153 g, 75.88 mmol) and triethylamine (20.14 mL, 14.62 g, 144.50 mmol) were added consecutively. The reaction

mixture was stirred for 18 hours at room temperature, poured into water (1.5 L) and stirred for an additional 1 hour. The crude product was filtered off and dissolved in dichloromethane (500 mL). The organic phase was washed with water (2 x 250 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration yielded a solid which was triturated in heptanes (200 mL). Filtration furnished 3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole (31.5 g) which was used without further purification.

^{1}H-NMR ($CDCl_3$): δ 8.87 (1H, d), 8.28 (1H, bs), 8.22 (1H, dd), 8.13 (1H, d), 7.49 (1H, d), 7.47-7.19 (18H, m); HPLC-MS (Method C): m/z: 243 (triphenylmethyl); Rt = 5.72 min.

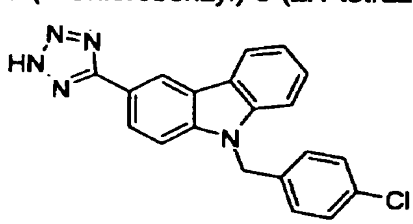
3-[2-(Triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole (200 mg, 0.42 mmol) was dissolved in methyl sulfoxide (1.5 mL). Sodium hydride (34 mg, 60 %, 0.85 mmol) was added, and the resulting suspension was stirred for 30 min at room temperature. 3-Chlorobenzyl chloride (85 µL, 108 mg, 0.67 mmol) was added, and the stirring was continued at 40 °C for 18 hours. The reaction mixture was cooled to ambient temperature and poured into 0.1 N hydrochloric acid (aq.) (15 mL). The precipitated solid was filtered off and washed with water (3 x 10 mL) to furnish 9-(3-chlorobenzyl)-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole, which was dissolved in a mixture of tetrahydrofuran and 6 N hydrochloric acid (aq.) (9:1) (10 mL) and stirred at room temperature for 18 hours. The reaction mixture was poured into water (100 mL). The solid was filtered off and rinsed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) to yield the title compound (127 mg). No further purification was necessary.

^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.36-7.27 (4H, m), 7.08 (1H, bt), 5.78 (2H, s); HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.07 min.

The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. aqueous sodium hydroxide (1 N) or by chromatography.

Example 564 **(General Procedure (J)).**

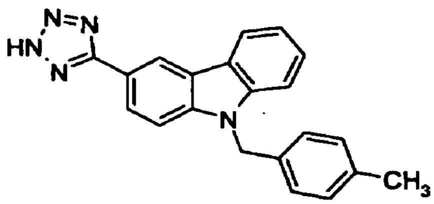
9-(4-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 360 (M+1); Rt = 4.31 min.

Example 565 **(General Procedure (J)).**

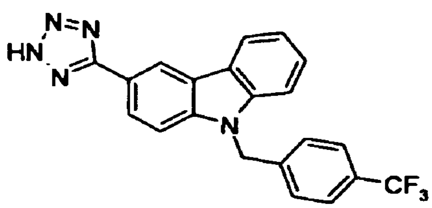
9-(4-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.26 min.

Example 566 **(General Procedure (J)).**

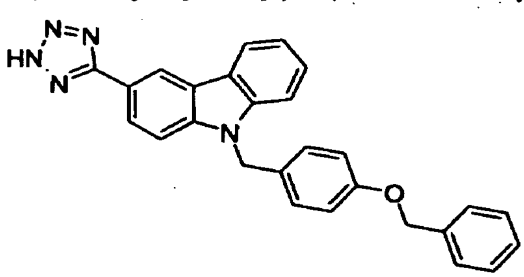
3-(2*H*-Tetrazol-5-yl)-9-(4-trifluoromethylbenzyl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.40 min.

Example 567 **(General Procedure (J)).**

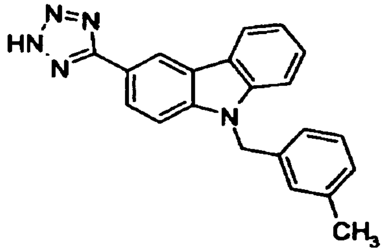
9-(4-Benzyloxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 432 (M+1); Rt = 4.70 min.

Example 568 **(General Procedure (J)).**

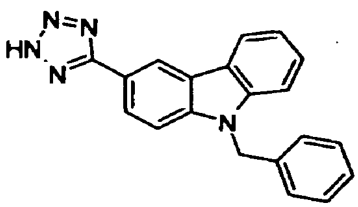
9-(3-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.25 min.

Example 569 **(General Procedure (J)).**

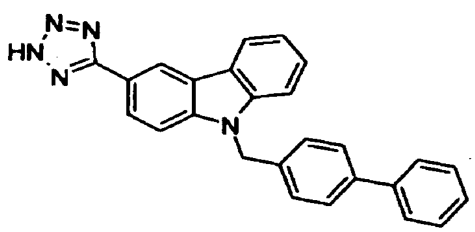
9-Benzyl-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.91 (1H, dd), 8.30 (1H, d), 8.13 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.53 (1H, t), 7.36-7.20 (6H, m), 5.77 (2H, s).

Example 570 **(General Procedure (J)).**

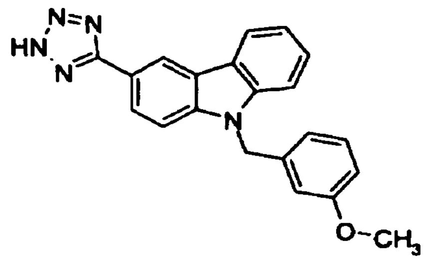
9-(4-Phenylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.94 (1H, s), 8.33 (1H, d), 8.17 (1H, dd), 7.95 (1H, d), 7.77 (1H, d), 7.61-7.27 (11H, m), 5.82 (2H, s).

Example 571 **(General Procedure (J)).**

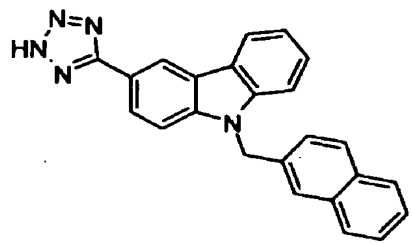
9-(3-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 356 (M+1); Rt = 3.99 min.

Example 572 **(General Procedure (J)).**

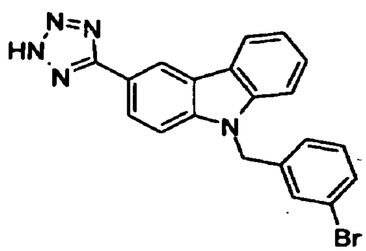
9-(Naphthalen-2-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.48 min.

Example 573 **(General Procedure (J)).**

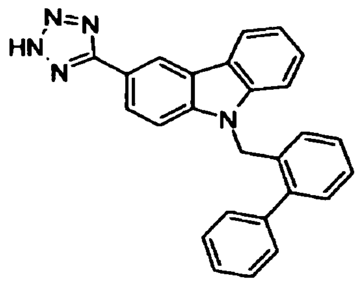
9-(3-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.33 min.

Example 574 **(General Procedure (J)).**

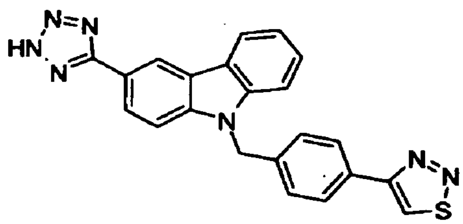
9-(Biphenyl-2-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 402 (M+1); Rt = 4.80 min.

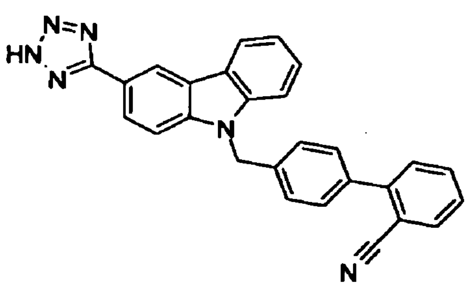
Example 575 **(General Procedure (J)).**

3-(2*H*-Tetrazol-5-yl)-9-[4-(1,2,3-thiadiazol-4-yl)benzyl]-9*H*-carbazole



Example 576 **(General Procedure (J)).**

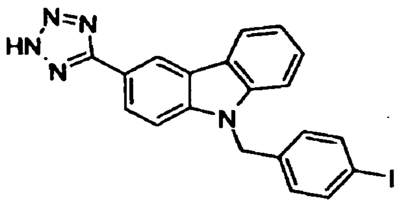
9-(2'-Cyanobiphenyl-4-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.91 (1H, d), 8.31 (1H, d), 8.13 (1H, dd), 7.95 (1H, d), 7.92 (1H, d), 7.78 (1H, d), 7.75 (1H, dt), 7.60-7.47 (5H, m), 7.38-7.28 (3H, m), 5.86 (2H, s); HPLC-MS (Method C): m/z: 427 (M+1); Rt = 4.38 min.

Example 577 **(General Procedure (J)).**

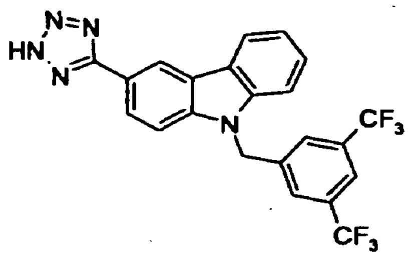
9-(4-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.37 min.

Example 578 **(General Procedure (J)).**

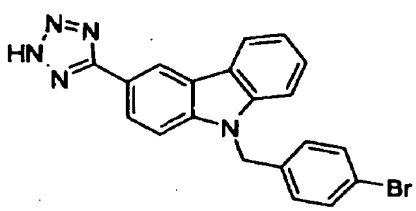
9-(3,5-Bis(trifluoromethyl)benzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.70 min.

Example 579 **(General Procedure (J)).**

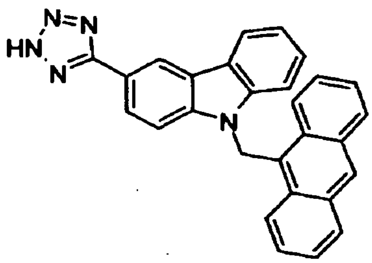
9-(4-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.70 (1H, d), 7.52 (1H, t), 7.49 (2H, d), 7.31 (1H, t), 7.14 (2H, d), 5.74 (2H, s); HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.40 min.

Example 580 **(General *Procedure (J)).***

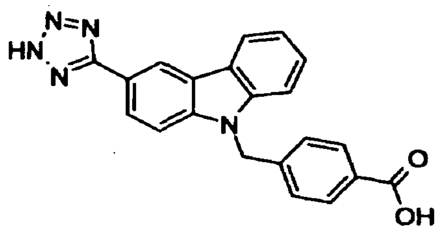
9-(Anthracen-9-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 426 (M+1); Rt = 4.78 min.

Example 581 **(General Procedure (J)).**

9-(4-Carboxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

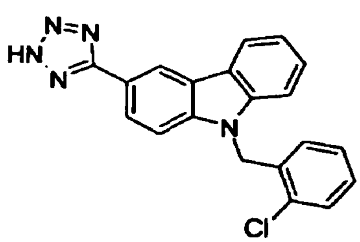


3.6 fold excess sodium hydride was used.

^{1}H-NMR (DMSO-d_6): δ 12.89 (1H, bs), 8.89 (1H, d), 8.30 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.86 (2H, d), 7.68 (1H, d), 7.51 (1H, t), 7.32 (1H, t), 7.27 (2H, d), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.37 min.

Example 582 **(General Procedure (J)).**

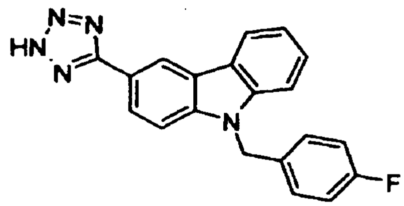
9-(2-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.30 min.

Example 583 **(General Procedure (J)).**

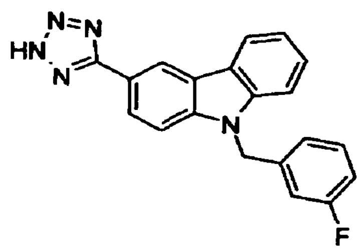
9-(4-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.88 (1H, d), 8.28 (1H, d), 8.10 (1H, dd), 7.89 (1H, d), 7.72 (1H, d), 7.52 (1H, t), 7.31 (1H, t), 7.31-7.08 (4H, m), 5.74 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

Example 584 **(General Procedure (J)).**

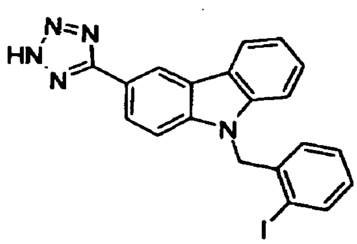
9-(3-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.37-7.27 (2H, m), 7.12-7.02 (2H, m), 6.97 (1H, d), 5.78 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

Example 585 **(General Procedure (J)).**

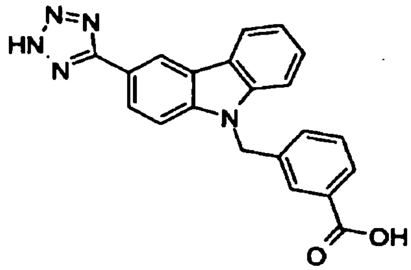
9-(2-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.58 min.

Example 586 **(General Procedure (J)).**

9-(3-Carboxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

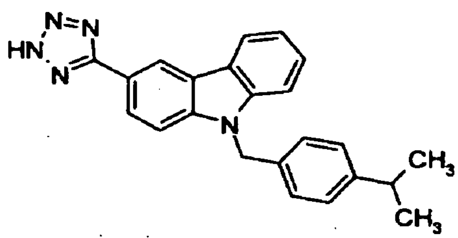


3.6 fold excess sodium hydride was used.

^{1}H-NMR (DMSO-d_6): δ 12.97 (1H, bs), 8.90 (1H, bs), 8.30 (1H, d), 8.12 (1H, bd), 7.89 (1H, d), 7.82 (1H, m), 7.77 (1H, bs), 7.71 (1H, d), 7.53 (1H, t), 7.46-7.41 (2H, m), 7.32 (1H, t), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.35 min.

Example 587 **(General Procedure (J)).**

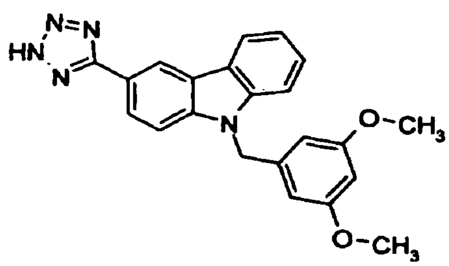
9-[4-(2-Propyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.27 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.71 (1H, d), 7.51 (1H, t), 7.31 (1H, t), 7.15 (2H, d), 7.12 (2H, d), 5.69 (2H, s), 2.80 (1H, sept), 1.12 (6H, d); HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.73 min.

Example 588 **(General Procedure (J)).**

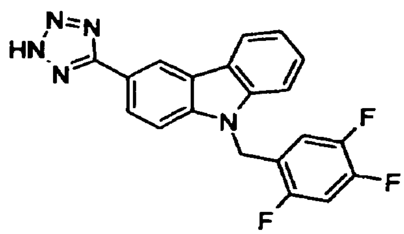
9-(3,5-Dimethoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 386 (M+1); Rt = 4.03 min.

Example 589 **(General Procedure (J)).**

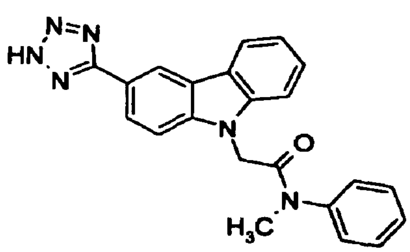
3-(2*H*-Tetrazol-5-yl)-9-(2,4,5-trifluorobenzyl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 380 (M+1); Rt = 5.00 min.

Example 590 **(General Procedure (J)).**

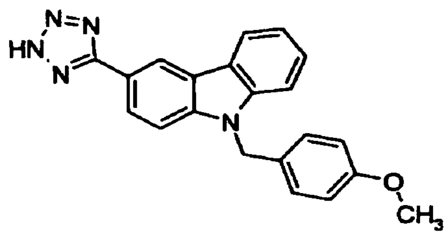
N-Methyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 383 (M+1); Rt = 4.30 min.

Example 591 **(General Procedure (J)).**

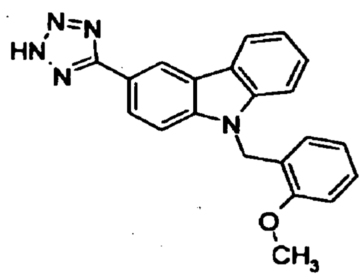
9-(4-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.86 (1H, d), 8.26 (1H, d), 8.10 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.51 (1H, t), 7.30 (1H, t), 7.18 (2H, d), 6.84 (2H, d), 5.66 (2H, s), 3.67 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.73 min.

Example 592 **(General Procedure (J)).**

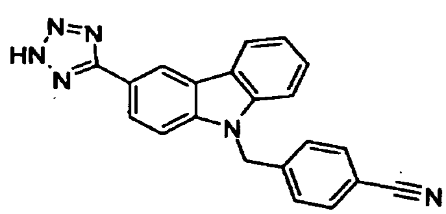
9-(2-Methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.27 (1H, d), 8.09 (1H, dd), 7.77 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.23 (1H, bt), 7.07 (1H, bd), 6.74 (1H, bt), 6.61 (1H, bd), 5.65 (2H, s), 3.88 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.97 min.

Example 593 **(General Procedure (J)).**

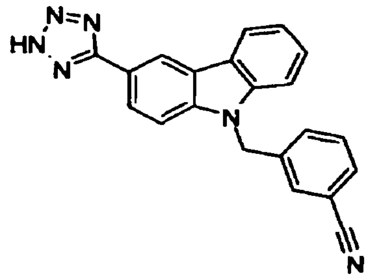
9-(4-Cyanobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.74 min.

Example 594 **(General Procedure (J)).**

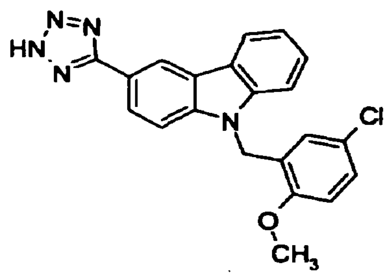
9-(3-Cyanobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.73 min.

Example 595 **(General Procedure (J)).**

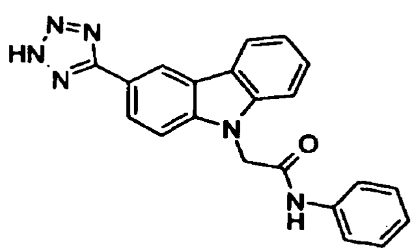
9-(5-Chloro-2-methoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.87 (1H, d), 8.35 (1H, d), 8.10 (1H, dd), 7.73 (1H, d), 7.59 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.27 (1H, dd), 7.11 (1H, d), 6.51 (1H, d), 5.63 (2H, s), 3.88 (3H, s); HPLC-MS (Method C): m/z: 390 (M+1); Rt = 4.37 min.

Example 596 **(General Procedure (J)).**

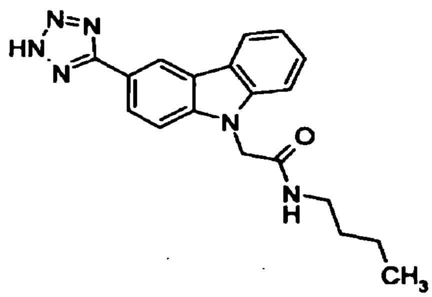
N-Phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



^{1}H-NMR (DMSO-d_6): δ 10.54 (1H, s), 8.87 (1H, bs), 8.27 (1H, d), 8.12 (1H, bd), 7.83 (1H, d), 7.66 (1H, d), 7.61 (2H, d), 7.53 (1H,t), 7.32 (1H, t), 7.32 (2H, t), 7.07 (1H, t), 5.36 (2H, s); HPLC-MS (Method C): m/z: 369 (M+1); Rt = 3.44 min.

Example 597 **(General Procedure (J)).**

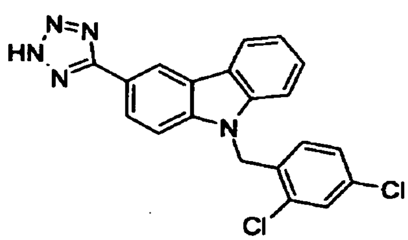
N-Butyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



^{1}H-NMR (DMSO-d_6): δ 8.85 (1H, d), 8.31 (1H, t), 8.25 (1H, d), 8.10 (1H, dd), 7.75 (1H, d), 7.58 (1H, d), 7.52 (1H, t), 7.30 (1H, t), 5.09 (2H, s), 3.11 (2H, q), 1.42 (2H, quint), 1.30 (2H, sext), 0.87 (3H, t); HPLC-MS (Method C): m/z: 349 (M+1); Rt = 3.20 min.

Example 598 **(General Procedure (J)).**

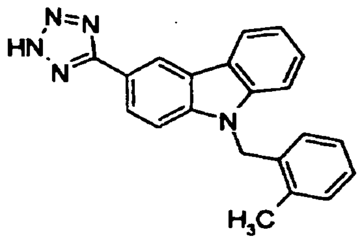
9-(2,4-Dichlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.92 (1H, d), 8.32 (1H, d), 8.09 (1H, dd), 7.76 (1H, d), 7.74 (1H, d), 7.58 (1H, d), 7.51 (1H, t), 7.33 (1H, t), 7.23 (1H, dd), 6.42 (1H, d), 5.80 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.87 min.

Example 599 **(General Procedure (J)).**

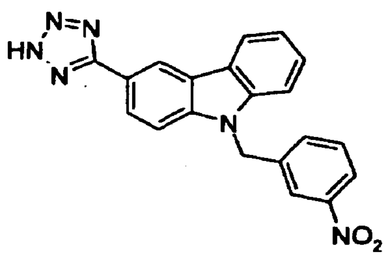
9-(2-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.92 (1H, d), 8.32 (1H, d), 8.08 (1H, dd), 7.72 (1H, d), 7.55 (1H, d), 7.48 (1H, t), 7.32 (1H, t), 7.26 (1H, d), 7.12 (1H, t), 6.92 (1H, t), 6.17 (1H, d), 5.73 (2H, s), 2.46 (3H, s); HPLC-MS (Method B): m/z: 340 (M+1); Rt = 5.30 min.

Example 600 **(General Procedure (J)).**

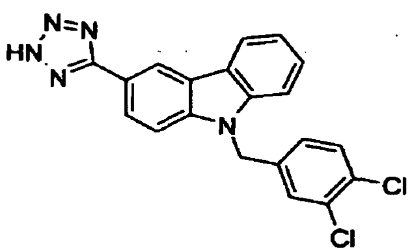
9-(3-Nitrobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 371 (M+1); Rt = 3.78 min.

Example 601 **(General Procedure (J)).**

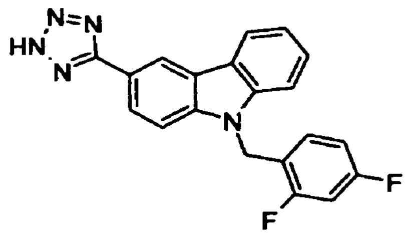
9-(3,4-Dichlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.62 min.

Example 602 **(General Procedure (J)).**

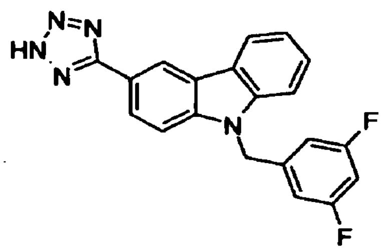
9-(2,4-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.69 (1H, d), 7.52 (1H, t), 7.36-7.24 (2H, m), 7.06-6.91 (2H, m), 5.78 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 603 **(General Procedure (J)).**

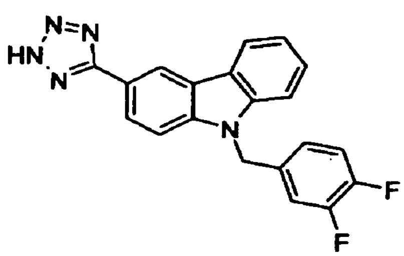
9-(3,5-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.90 (1H, bs), 8.31 (1H, d), 8.13 (1H, bd), 7.90 (1H, d), 7.73 (1H, d), 7.54 (1H, t), 7.34 (1H, t), 7.14 (1H, t), 6.87 (2H, bd), 5.80 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 604 **(General Procedure (J)).**

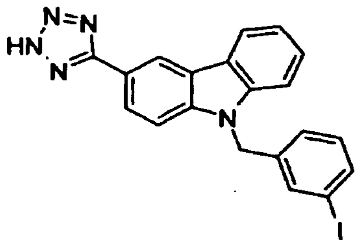
9-(3,4-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, bs), 8.29 (1H, d), 8.12 (1H, bd), 7.92 (1H, d), 7.74 (1H, d), 7.54 (1H, t), 7.42-7.25 (3H, m), 6.97 (1H, bm), 5.75 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 605 **(General Procedure (J)).**

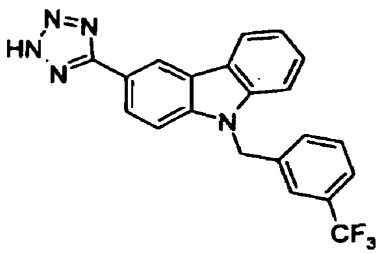
9-(3-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method B): m/z: 452 (M+1); Rt = 5.50 min.

Example 606 **(General Procedure (J)).**

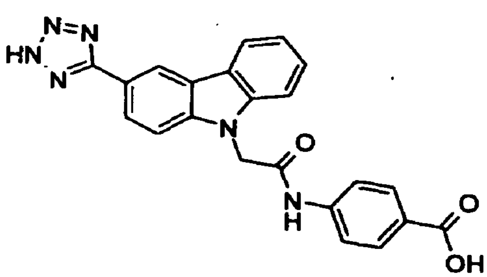
3-(2*H*-Tetrazol-5-yl)-9-[3-(trifluoromethyl)benzyl]-9*H*-carbazole



^{1}H-NMR (DMSO-d_6): δ 8.89 (1H, d), 8.30 (1H, d), 8.11 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.67 (1H, bs), 7.62 (1H, bd), 7.53 (1H, t), 7.50 (1H, bt), 7.33 (1H, bd), 7.32 (1H, t), 5.87 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.40 min.

Example 607 **(General Procedure (J)).**

N-(4-Carboxyphenyl)-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide

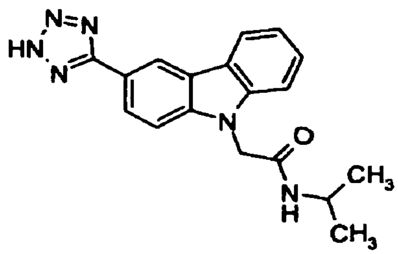


3.6 fold excess sodium hydride was used.

HPLC-MS (Method B): m/z: 413 (M+1); Rt = 3.92 min.

Example 608 **(General Procedure (J)).**

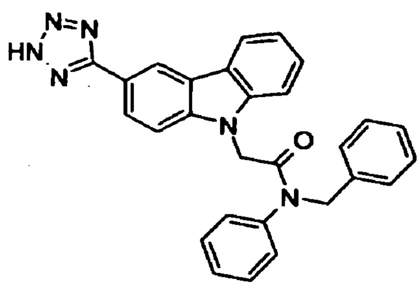
N-(2-Propyl)-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 335 (M+1); Rt = 3.70 min.

Example 609 **(General Procedure (J)).**

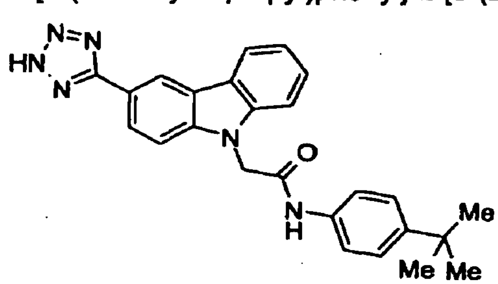
N-Benzyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 459 (M+1); Rt = 5.37 min.

Example 610 **(General Procedure (J)).**

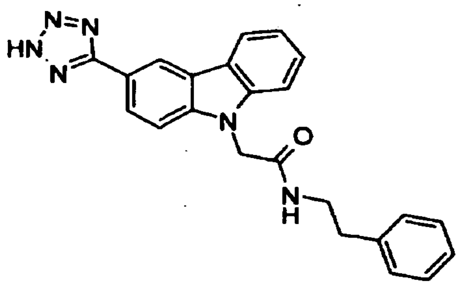
N-[4-(2-Methyl-2-propyl)phenyl]-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 425 (M+1); Rt = 5.35 min.

Example 611 **(General Procedure (J)).**

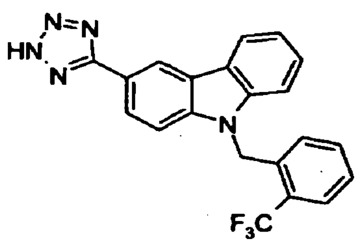
N-Phenethyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method C): m/z: 397 (M+1); Rt = 3.43 min.

Example 612 **(General Procedure (J)).**

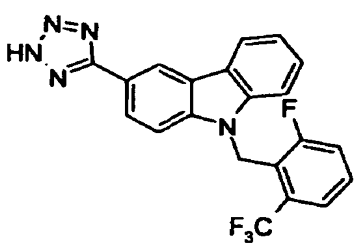
3-(2*H*-Tetrazol-5-yl)-9-[2-(trifluoromethyl)benzyl]-9*H*-carbazole



HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.44 min.

Example 613 **(General Procedure (J)).**

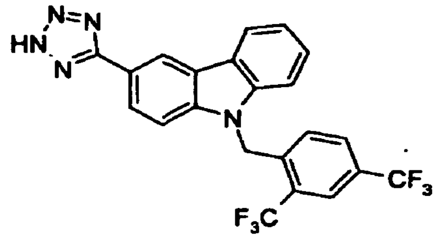
9-[2-Fluoro-6-(trifluoromethyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.21 min.

Example 614 **(General Procedure (J)).**

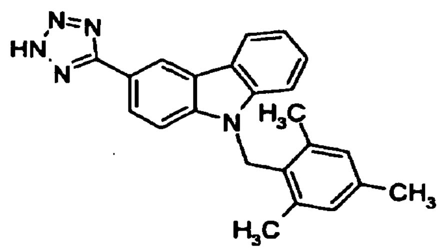
9-[2,4-Bis(trifluoromethyl)benzyl)]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.82 min.

Example 615 **(General Procedure (J)).**

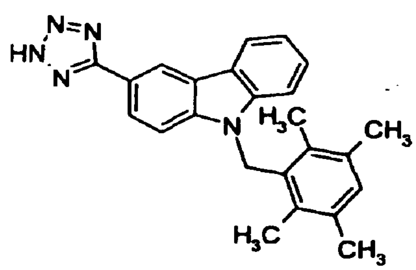
3-(2*H*-Tetrazol-5-yl)-9-(2,4,6-trimethylbenzyl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.59 min.

Example 616 **(General Procedure (J)).**

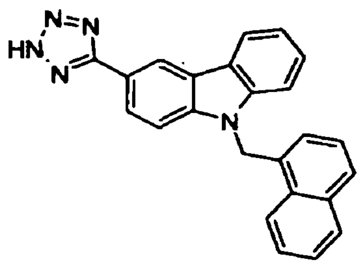
9-(2,3,5,6-Tetramethylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 382 (M+1); Rt = 4.47 min.

Example 617 **(General Procedure (J)).**

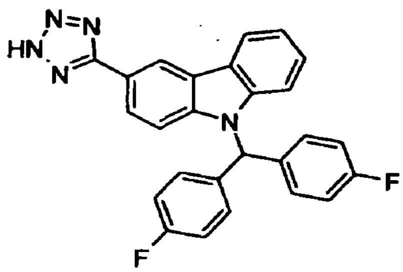
9-[(Naphthalen-1-yl)methyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.43 min.

Example 618 **(General Procedure (J)).**

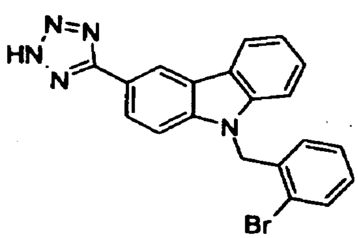
9-[Bis(4-fluorophenyl)methyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 438 (M+1); Rt = 4.60 min.

Example 619 **(General Procedure (J)).**

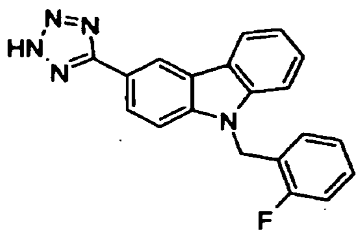
9-(2-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.50 min.

Example 620 **(General Procedure (J)).**

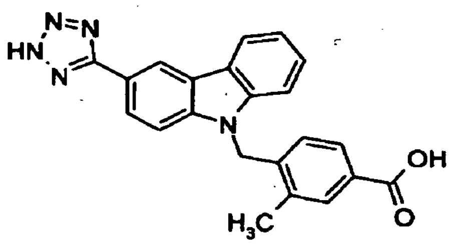
9-(2-Fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.09 min.

Example 621 **(General Procedure (J)).**

9-(4-Carboxy-2-methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

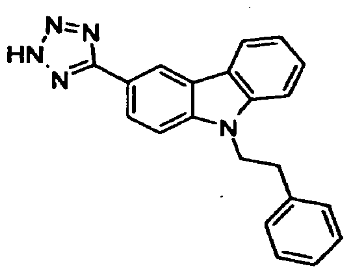


In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.56 min.

Example 622 **(General Procedure (J)).**

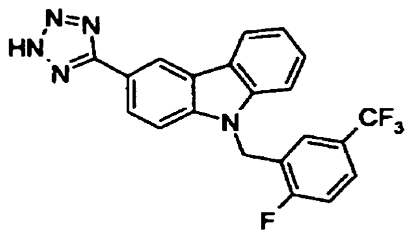
9-(2-Phenylethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.08 min.

Example 623 **(General Procedure (J)).**

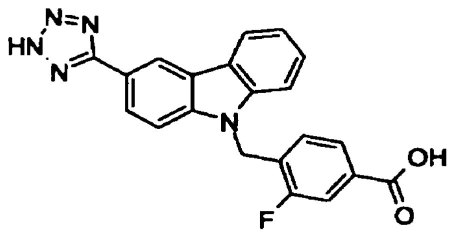
9-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.34 min.

Example 624 **(General Procedure (J)).**

9-(4-Carboxy-2-fluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

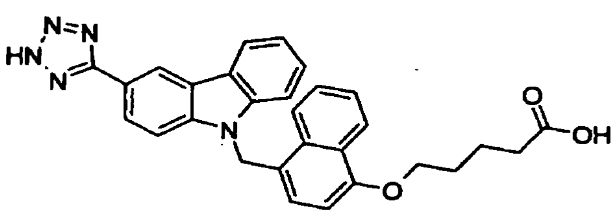


3-Fluoro-4-methylbenzoic acid (3.0 g, 19.5 mmol) and benzoyl peroxide (0.18 g, 0.74 mmol) were suspended in benzene. The mixture was purged with N_2 and heated to reflux. *N*-Bromosuccinimide (3.47 g, 19.5 mmol) was added portionwise, and reflux was maintained for 18 hours. The reaction mixture was concentrated, and the residue was washed with water (20 mL) at 70 °C for 1 hour. The crude product was isolated by filtration and washed with additional water (2 x 10 mL). The dry product was recrystallized from heptanes. Filtration furnished 4-bromomethyl-3-fluorobenzoic acid (1.92 g) which was used in the following step according to General Procedure (J).

In this preparation, a 3.6-fold excess of sodium hydride was used.
HPLC-MS (Method C): m/z: 388 (M+1); Rt = 3.49 min.

Example 625 **(General Procedure (J)).**

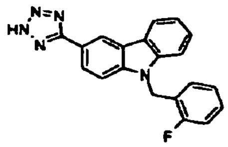
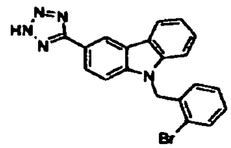
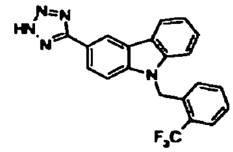
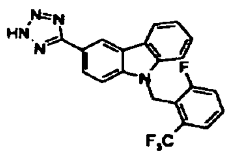
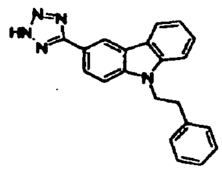
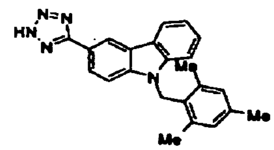
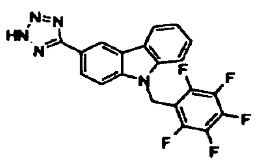
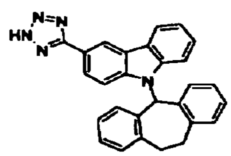
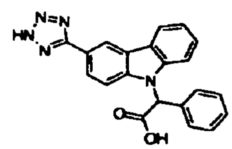
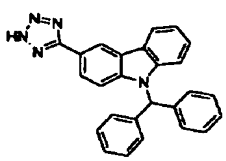
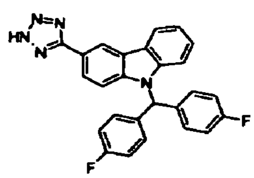
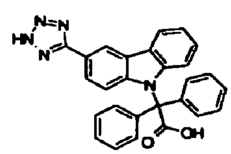
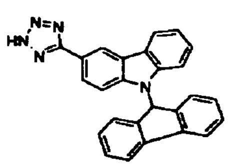
5-{4-[[(3-(2*H*-Tetrazol-5-yl)carbazol-9-yl)methyl]naphthalen-1-yl]oxy}pentanoic Acid



5-[(4-Formylnaphthalen-1-yl)oxy]pentanoic acid intermediate obtained in example 302(3.0 g, 11.0 mmol) was dissolved in a mixture of methanol and tetrahydrofuran (9:1) (100 mL), and sodium borohydride (1.67 g, 44.1 mmol) was added portionwise at ambient temperature. After 30 minutes, the reaction mixture was concentrated to 50 mL and added to hydrochloric acid (0.1 N, 500 mL). Additional hydrochloric acid (1 N, 40 mL) was added, and 5-[(4-hydroxymethyl-naphthalen-1-yl)oxy]pentanoic acid (2.90 g) was collected by filtration. To the crude product was added concentrated hydrochloric acid (100 mL), and the suspension was stirred vigorously for 48 hours at room temperature. The crude product was filtered off and washed with water, until the pH was essentially neutral. The material was washed with heptanes to furnish 5-[(4-chloromethylnaphthalen-1-yl)oxy]pentanoic acid (3.0 g) which was used in the following step according to General Procedure (J).

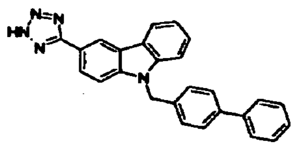
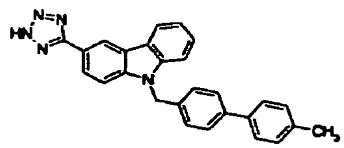
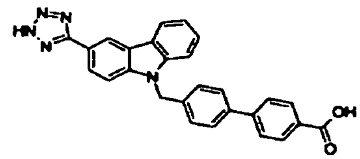
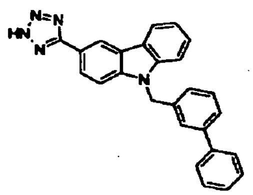
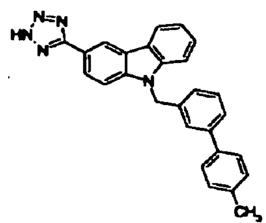
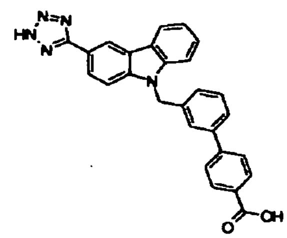
In this preparation, a 3.6-fold excess of sodium hydride was used.
HPLC-MS (Method C): m/z: 492 (M+1); Rt = 4.27 min.

Further compounds of the invention that may be prepared according to general procedure (J), and includes:

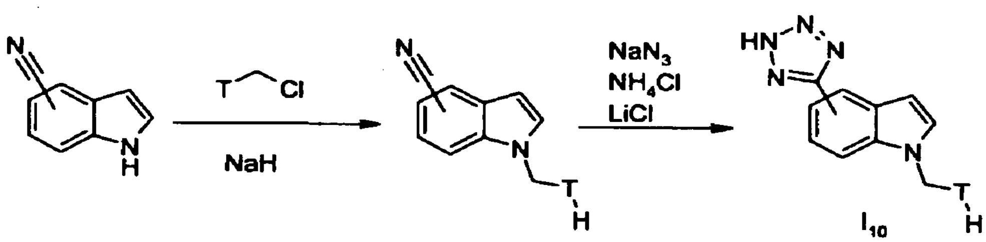
Example 626 	**Example 627** 	**Example 628** 
Example 629 	**Example 630** 	**Example 631** 
Example 632 	**Example 633** 	**Example 634** 
Example 635 	**Example 636** 	**Example 637** 
Example 638 		

The following compounds of the invention may be prepared eg. from 9-(4-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 579) or from 9-(3-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 573) and aryl boronic acids *via* the Suzuki coupling reaction eg as described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited

therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(tri-*tert*-butylphosphine)palladium (0).

Example 639 	**Example 640** 	**Example 641** 
Example 642 	**Example 643** 	**Example 644** 

General procedure (K) for preparation of compounds of general formula I_{10}:

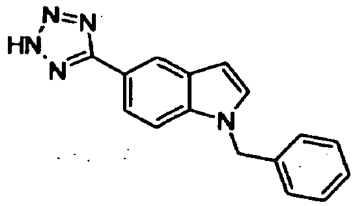


I_{10}

wherein T is as defined above.

The general procedure (K) is further illustrated by the following example:

Example 645 **(General procedure (K)).** 1-Benzyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole



5-Cyanoindole (1.0 g, 7.0 mmol) was dissolved in *N,N*-dimethylformamide (14 mL) and cooled in an ice-water bath. Sodium hydride (0.31 g, 60 %, 7.8 mmol) was added, and the resulting suspension was stirred for 30 min. Benzyl chloride (0.85 mL, 0.94 g, 7.4 mmol) was added, and the cooling was discontinued. The stirring was continued for 65 hours at room temperature. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with brine (30 mL) and dried with sodium sulfate (1 hour). Filtration and concentration yielded the crude material. Purification by flash chromatography on silica gel eluting with ethyl acetate/heptanes = 1:3 afforded 1.60 g 1-benzyl-1*H*-indole-5-carbonitrile.

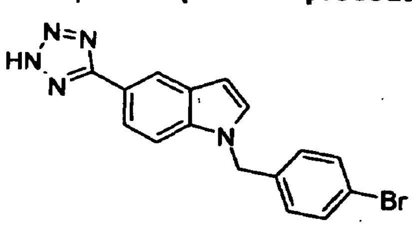
HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.17 min.

1-Benzyl-1*H*-indole-5-carbonitrile was transformed into 1-benzyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in general procedure (J) and in example **437**. Purification was done by flash chromatography on silica gel eluting with dichloromethane/methanol = 9:1.

HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.35 min.

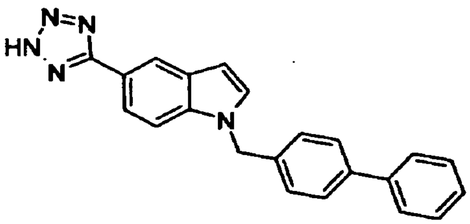
The compounds in the following examples were prepared by the same procedure.

Example 646 **(General procedure (K)).** 1-(4-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method C): m/z: 354 (M+1); Rt = 3.80 min.

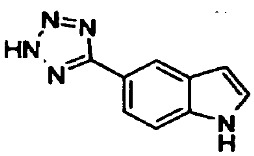
Example 647 **(General procedure (K)).**1-(4-Phenylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 5.52 (2H, s), 6.70 (1H, d), 7.3-7.45 (6H, m), 7.6 (4H, m), 7.7-7.8 (2H, m), 7.85(1H, dd), 8.35 (1H, d).

Calculated for $C_{22}H_{17}N_5$, H_2O:
73.32% C; 5.03% H; 19.43% N. Found:
73.81% C; 4.90% H; 19.31% N.

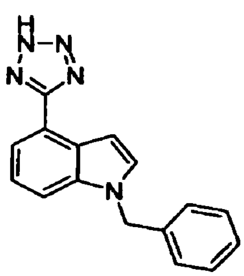
Example 648 **(General procedure (K)).**5-(2*H*-Tetrazol-5-yl)-1*H*-indole



5-(2*H*-Tetrazol-5-yl)-1*H*-indole was prepared from 5-cyanoindole according to the method described in example 437.

HPLC-MS (Method C): m/z: 186 (M+1); Rt = 1.68 min.

Example 649 **(General procedure (K)).**1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole

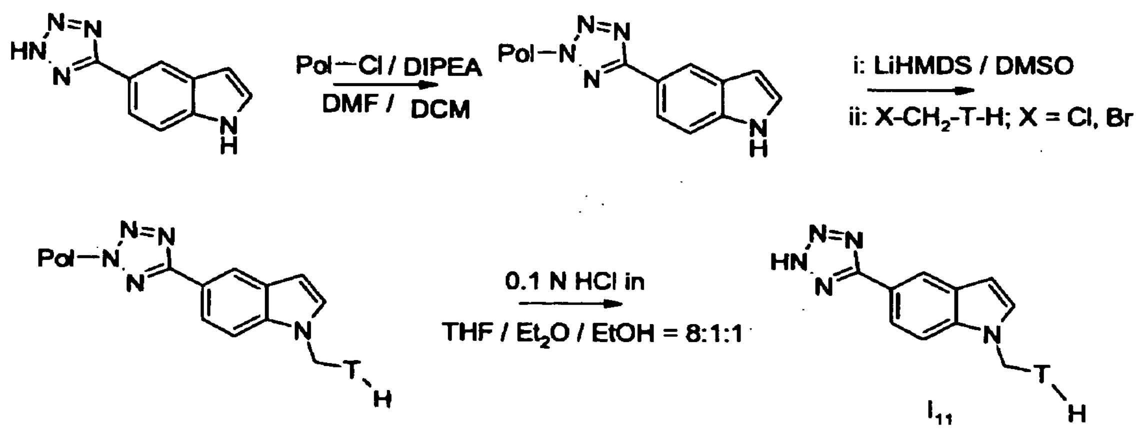


1-Benzyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 645.
HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.24 min.

1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzyl-1*H*-indole-4-carbonitrile according to the method described in example 437.

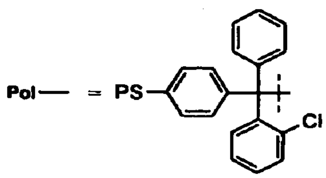
HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.44 min.

General procedure (L) for preparation of compounds of general formula I_{11}:



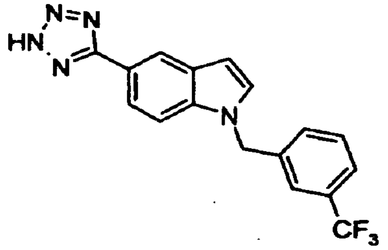
wherein T is as defined above and

Pol- is a polystyrene resin loaded with a 2-chlorotrityl linker, graphically shown below:



This general procedure (L) is further illustrated by the following example:

Example 650 **(General procedure (L))**.5-(2*H*-Tetrazol-5-yl)-1-[3-(trifluoromethyl)benzyl]-1*H*-indole

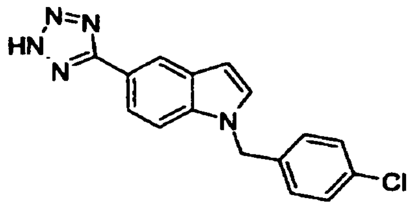


2-Chlorotritylchloride resin (100 mg, 0.114 mmol active chloride) was swelled in dichloromethane (2 mL) for 30 min. The solvent was drained, and a solution of 5-(2*H*-tetrazol-5-yl)-1*H*-indole (example 648) (63 mg, 0.34 mmol) in a mixture of *N,N*-dimethylformamide, dichloromethane and *N,N*-di(2-propyl)ethylamine (DIPEA) (5:5:2) (1.1 mL) was added. The reaction mixture was shaken at room temperature for 20 hours. The solvent was removed by filtration, and the resin was washed consecutively with *N,N*-dimethylformamide (2 x 4 mL), dichloromethane (6 x 4 mL) and methyl sulfoxide (2 x 4 mL). Methyl sulfoxide (1 mL) was added, followed by the addition of a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 0.57 mL, 0.57 mmol). The mixture was shaken for 30 min at room temperature, before 3-(trifluoromethyl)benzyl bromide (273 mg, 1.14 mmol) was added as a solution in methyl sulfoxide (0.2 mL). The reaction mixture was shaken for 20 hours at room temperature. The drained resin was washed consecutively with methyl sulfoxide (2 x 4 mL), dichloromethane (2 x 4 mL), methanol (2 x 4 mL), dichloromethane (2 x 4 mL) and tetrahydrofuran (4 mL). The resin was treated with a solution of hydrogen chloride in tetrahydrofuran, ethyl ether and ethanol = 8:1:1 (0.1 M, 3 mL) for 6 hours at room temperature. The resin was drained and the filtrate was concentrated *in vacuo*. The crude product was re-suspended in dichloromethane (1.5 mL) and concentrated three times to afford the title compound (35 mg). No further purification was necessary.

HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.35 min.
^{1}H-NMR (DMSO-d_6): δ 8.29 (1H, s), 7.80 (1H, dd), 7.72 (2H, m), 7.64 (2H, bs), 7.56 (1H, t), 7.48 (1H, d), 6.70 (1H, d), 5.62 (2H, s).

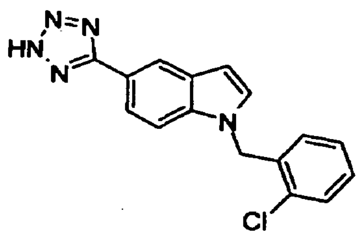
The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization or by chromatography.

Example 651 **(General procedure (L)).**1-(4-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



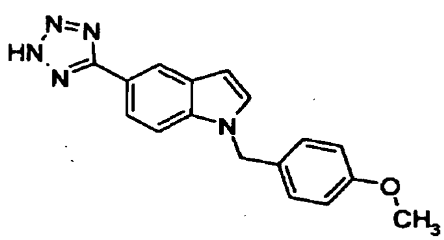
HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.11 min.

Example 652 **(General procedure (L)).**1-(2-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



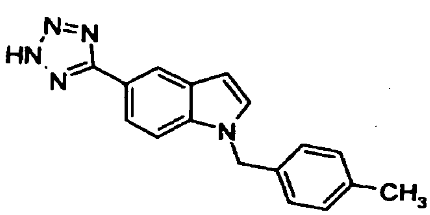
HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.05 min.

Example 653 **(General procedure (L)).AKP**1-(4-Methoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



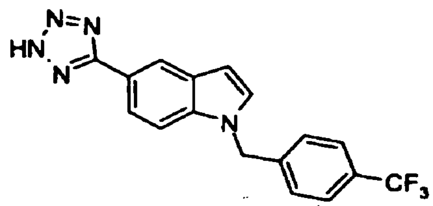
HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.68 min.

Example 654 **(General procedure (L)).AKP**1-(4-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



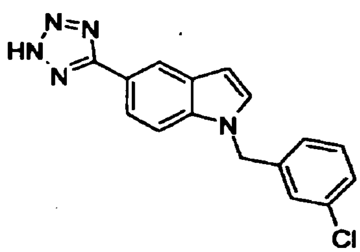
HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Example 655 **(General procedure (L)).AKP**5-(2*H*-Tetrazol-5-yl)-1-[4-(trifluoromethyl)benzyl]-1*H*-indole



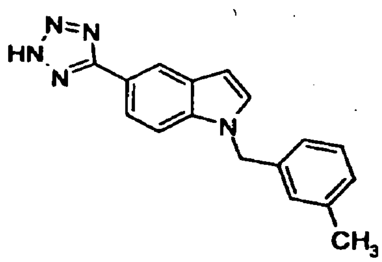
HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.18 min.

Example 656 **(General procedure (L)).AKP**1-(3-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



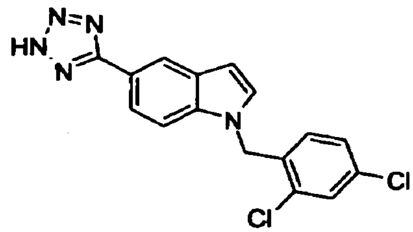
HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.01 min.

Example 657 **(General procedure (L)).AKP**1-(3-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



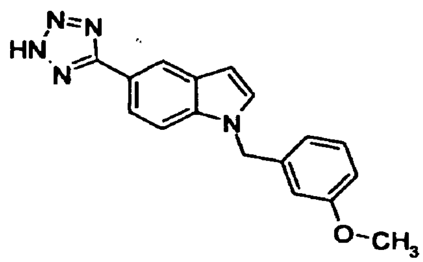
HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Example 658 **(General procedure (L)).AKP**1-(2,4-Dichlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



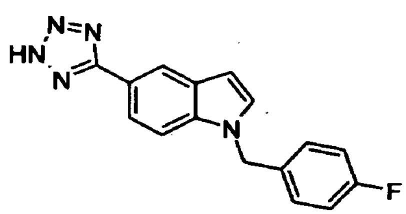
HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.41 min.

Example 659 **(General procedure (L)).AKP**1-(3-Methoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



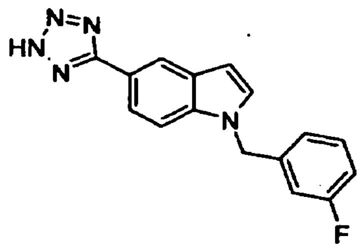
HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.64 min.

Example 660 **(General procedure (L)).AKP**1-(4-Fluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



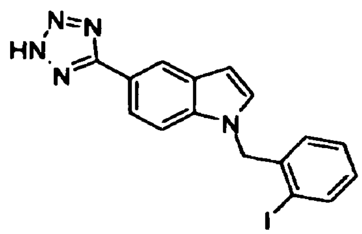
HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.71 min.

Example 661 **(General procedure (L)).AKP**1-(3-Fluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



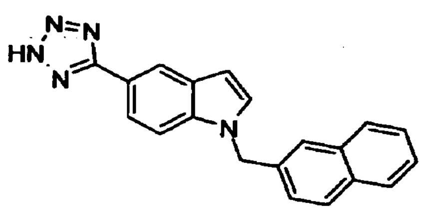
HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.68 min.

Example 662 **(General procedure (L)).AKP**1-(2-Iodobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



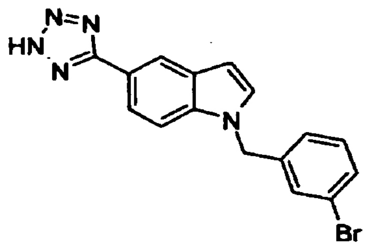
HPLC-MS (Method B): m/z: 402 (M+1); Rt = 4.11 min.

Example 663 **(General procedure (L)).AKP**1-[(Naphthalen-2-yl)methyl]-5-(2*H*-tetrazol-5-yl)-1*H*-indole



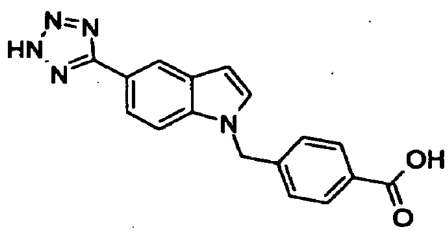
HPLC-MS (Method B): m/z: 326 (M+1); Rt = 4.18 min.

Example 664 **(General procedure (L)).AKP**1-(3-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.08 min.

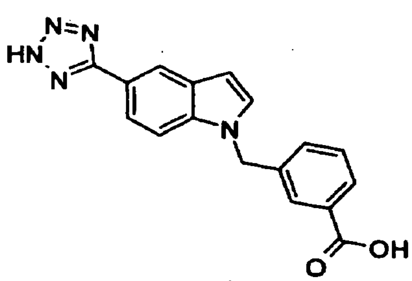
Example 665 **(General procedure (L)).AKP**1-(4-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.84 min.

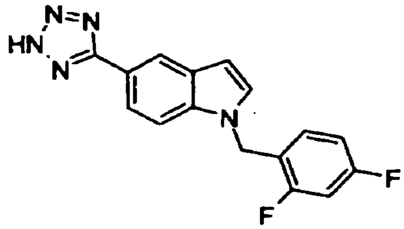
Example 666 **(General procedure (L)).AKP**1-(3-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

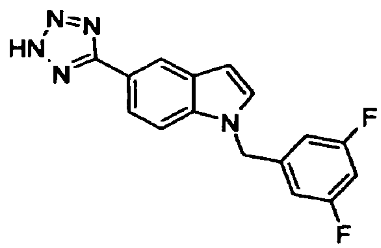
HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.91 min.

Example 667 **(General procedure (L)).AKP**1-(2,4-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



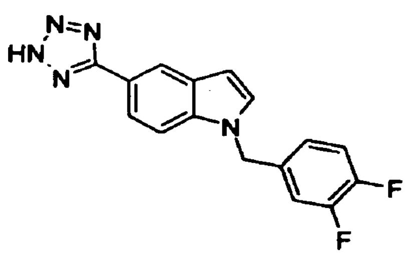
HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 668 **(General procedure (L)).AKP**1-(3,5-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



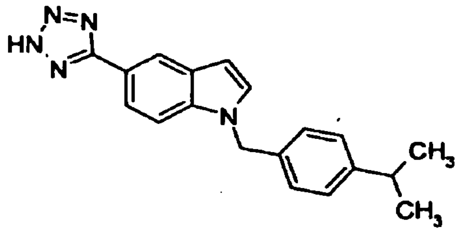
HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 669 **(General procedure (L)).AKP**1-(3,4-Difluorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



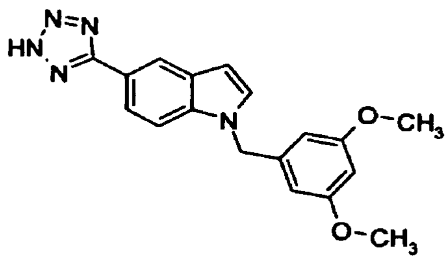
HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.81 min.

Example 670 **(General procedure (L)).AKP**1-[4-(2-Propyl)benzyl]-5-(2*H*-tetrazol-5-yl)-1*H*-indole



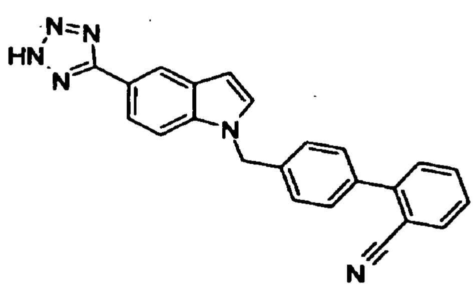
HPLC-MS (Method B): m/z: 318 (M+1); Rt = 4.61 min.

Example 671 **(General procedure (L)).AKP**1-(3,5-Dimethoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



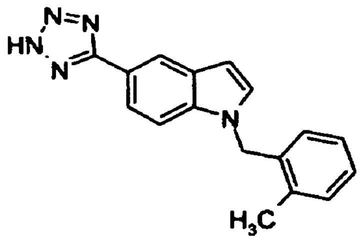
HPLC-MS (Method B): m/z: 336 (M+1); Rt = 3.68 min.

Example 672 **(General procedure (L)).AKP**1-(2'-Cyanobiphenyl-4-ylmethyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



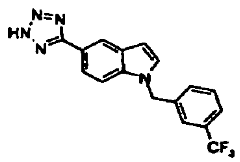
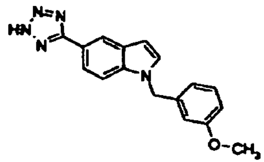
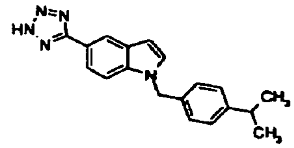
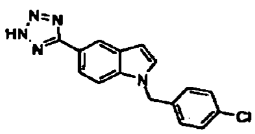
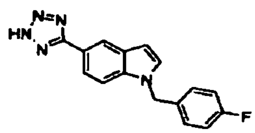
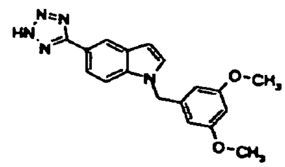
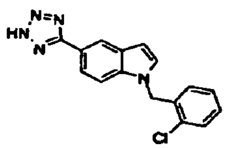
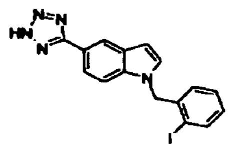
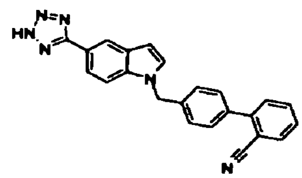
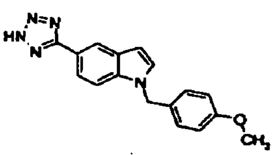
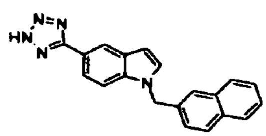
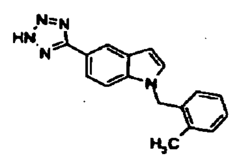
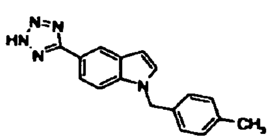
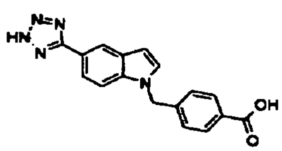
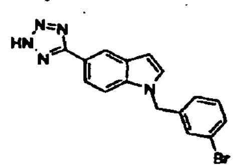
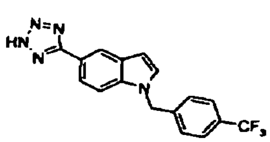
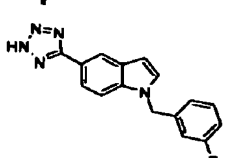
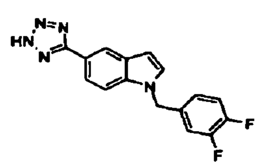
HPLC-MS (Method B): m/z: 377 (M+1); Rt = 4.11 min.

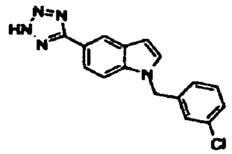
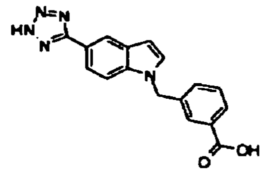
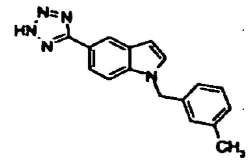
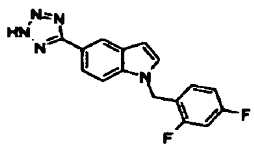
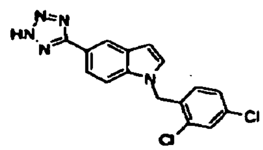
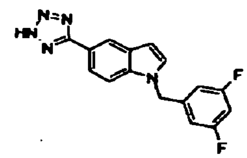
Example 673 **(General procedure (L)).AKP**1-(2-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



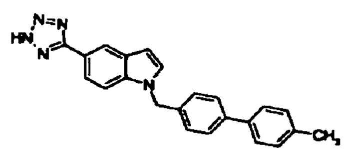
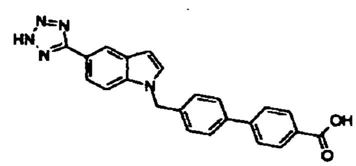
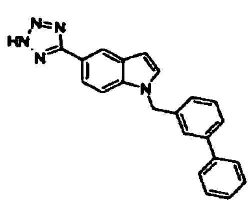
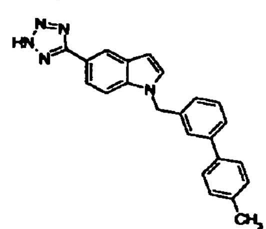
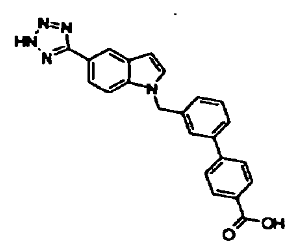
HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Further compounds of the invention that may be prepared according to general procedure (K) and/or (L) includes:

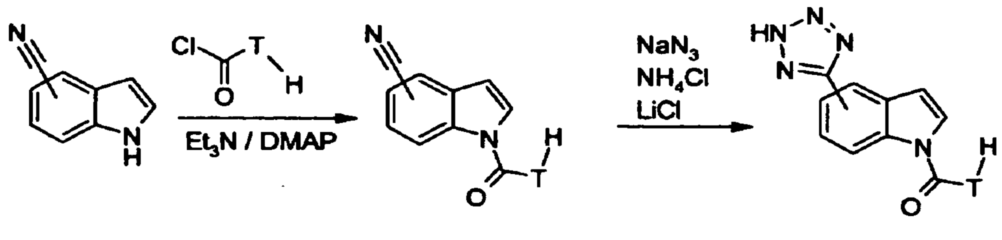
Example 674 	**Example 675** 	**Example 676** 
Example 677 	**Example 678** 	**Example 679** 
Example 680 	**Example 681** 	**Example 682** 
Example 683 	**Example 684** 	**Example 685** 
Example 686 	**Example 687** 	**Example 688** 
Example 689 	**Example 690** 	**Example 691** 

Example 692 	**Example 693** 	**Example 694** 
Example 695 	**Example 696** 	**Example 697** 

The following compounds of the invention may be prepared eg. from 1-(4-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole (example 646) or from the analogue 1-(3-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole and aryl boronic acids *via* the Suzuki coupling reaction eg as described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(tri-*tert*-butylphosphine)palladium (0).

	Example 698 	**Example 699** 
Example 700 	**Example 701** 	**Example 702** 

General procedure (M) for preparation of compounds of general formula I_{12}:

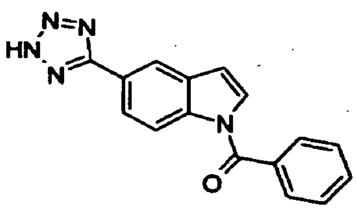


I_{12}

wherein T is as defined above.

The general procedure (M) is further illustrated by the following example:

Example 703 **(General procedure (M)).**1-Benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole



To a solution of 5-cyanoindole (1.0 g, 7.0 mmol) in dichloromethane (8 mL) was added 4-(dimethylamino)pyridine (0.171 g, 1.4 mmol), triethylamine (1.96 mL, 1.42 g, 14 mmol) and benzoyl chloride (0.89 mL, 1.08 g, 7.7 mmol). The resulting mixture was stirred for 18 hours at room temperature. The mixture was diluted with dichloromethane (80 mL) and washed consecutively with a saturated solution of sodium hydrogencarbonate (40 mL) and brine (40 mL). The organic phase was dried with magnesium sulfate (1 hour). Filtration and concentration furnished the crude material which was purified by flash chromatography on silica gel, eluting with ethyl acetate/heptanes = 2:3. 1-Benzoyl-1*H*-indole-5-carbonitrile was obtained as a solid.

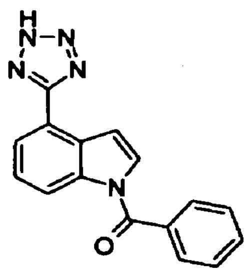
HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.07 min.

1-Benzoyl-1*H*-indole-5-carbonitrile was transformed into 1-benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in example 437.

HPLC (Method C): Rt = 1.68 min.

The compound in the following example was prepared by the same procedure.

Example 704 **(General procedure (M)).**1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole



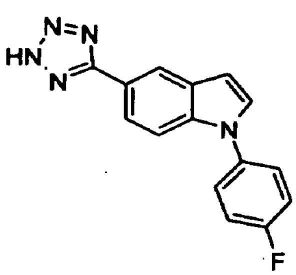
1-Benzoyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 703.
HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.24 min.

1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzoyl-1*H*-indole-4-carbonitrile according to the method described in example 437.

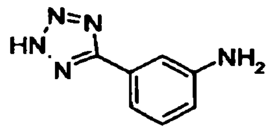
HPLC (Method C): Rt = 1.56 min.

The following known and commercially available compounds do all bind to the His B10 Zn^{2+} site of the insulin hexamer:

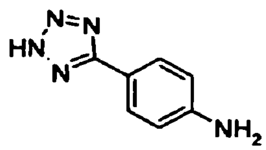
Example 7051-(4-Fluorophenyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



Example 7061-Amino-3-(2*H*-tetrazol-5-yl)benzene



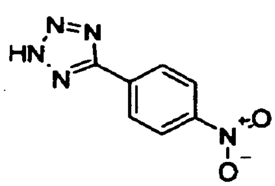
Example 7071-Amino-4-(2*H*-tetrazol-5-yl)benzene



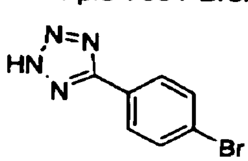
A mixture of 4-aminobenzonitrile (10 g, 84.6 mmol), sodium azide (16.5 g, 254 mmol) and ammonium chloride (13.6 g, 254 mmol) in DMF was heated at 125 °C for 16 hours. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was added water (200 mL) and diethyl ether (200 mL) which resulted in crystallisation. The mixture was filtered and the solid was dried *in vacuo* at 40 °C for 16 hours to afford 5-(4-aminophenyl)-2*H*-tetrazole.

^1H NMR DMSO-d_6): δ = 5.7 (3H, bs), 6.69 (2H, d), 7.69 (2H, d).
HPLC-MS (Method C): m/z: 162 (M+1); Rt = 0,55 min.

Example 7081-Nitro-4-(2*H*-tetrazol-5-yl)benzene

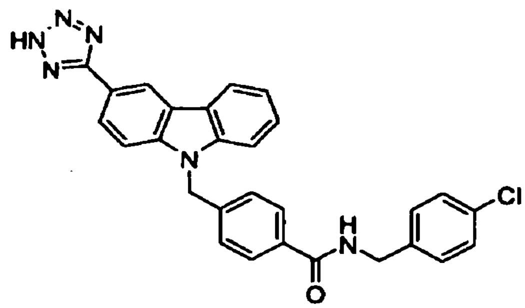


Example 7091-Bromo-4-(2*H*-tetrazol-5-yl)benzene



Example 710 **(General procedure (N))**

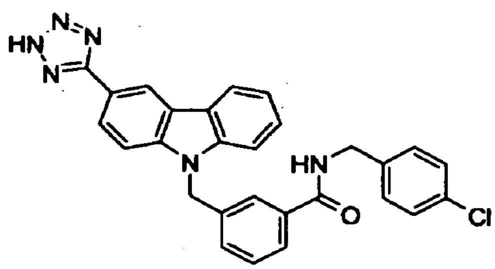
N-(4-Chlorobenzyl)-4-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z:493 (M+1); Rt = 4.19 min.

Example 711 **(General procedure (N))**

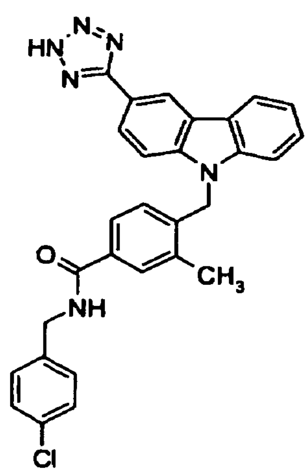
N-(4-Chlorobenzyl)-3-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z: 493 (M+1); Rt = 4.20 min.

Example 712 (General Procedure (N))

N-(4-Chlorobenzyl)-3-methyl-4-[3-(2*H*-tetrazol-5-yl)-carbazol-9-ylmethyl]benzamide

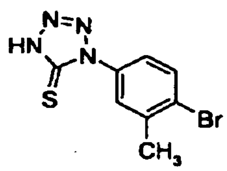


HPLC-MS (Method C): m/z: 507 (M+1); Rt = 4.37min.

The commercially available compounds in the following examples do all bind to the HisB10 Zn^{2+}site:

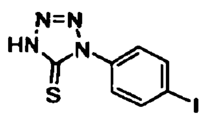
Example 713

1-(4-Bromo-3-methylphenyl)-1,4-dihydrotetrazole-5-thione



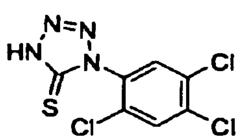
Example 714

1-(4-Iodophenyl)-1,4-dihydrotetrazole-5-thione



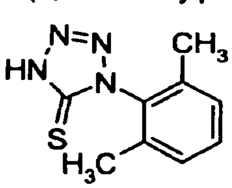
Example 715

1-(2,4,5-Trichlorophenyl)-1*H*-tetrazole-5-thiol



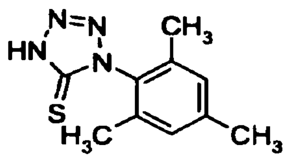
Example 716

1-(2,6-Dimethylphenyl)-1,4-dihydrotetrazole-5-thione



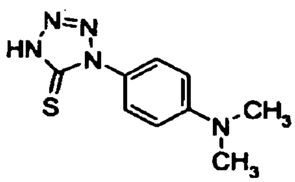
Example 717

1-(2,4,6-Trimethylphenyl)-1,4-dihydrotetrazole-5-thione



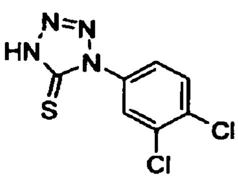
Example 718

1-(4-Dimethylaminophenyl)-1*H*-tetrazole-5-thiol



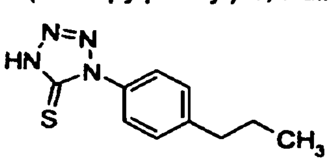
Example 719

1-(3,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



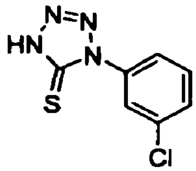
Example 720

1-(4-Propylphenyl)-1,4-dihydro-1H-tetrazole-5-thione



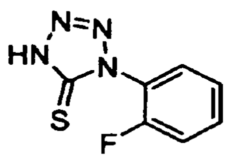
Example 721

1-(3-Chlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



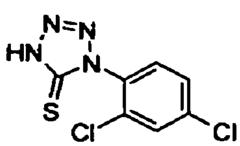
Example 722

1-(2-Fluorophenyl)-1,4-dihydro-1H-tetrazole-5-thione



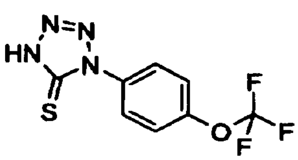
Example 723

1-(2,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



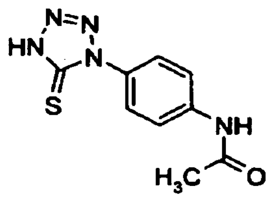
Example 724

1-(4-Trifluoromethoxyphenyl)-1,4-dihydro-1*H*-tetrazole-5-thione



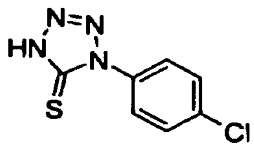
Example 725

N-[4-(5-Mercaptotetrazol-1-yl)-phenyl]-acetamide



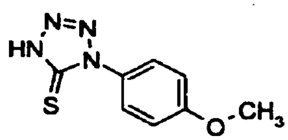
Example 726

1-(4-Chlorophenyl)-1,4-dihydrotetrazole-5-thione



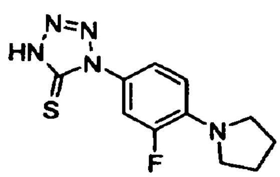
Example 727

1-(4-Methoxyphenyl)-1,4-dihydrotetrazole-5-thione



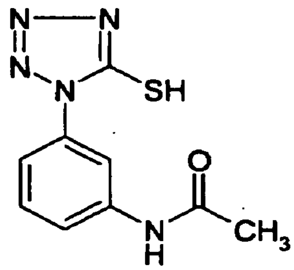
Example 728

1-(3-Fluoro-4-pyrrolidin-1-ylphenyl)-1,4-dihydrotetrazole-5-thione



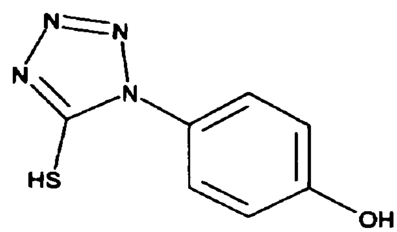
Example 729

N-[3-(5-Mercaptotetrazol-1-yl)phenyl]acetamide

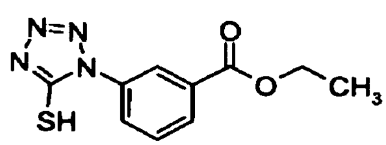


Example 730

1-(4-Hydroxyphenyl)-5-mercaptotetrazole

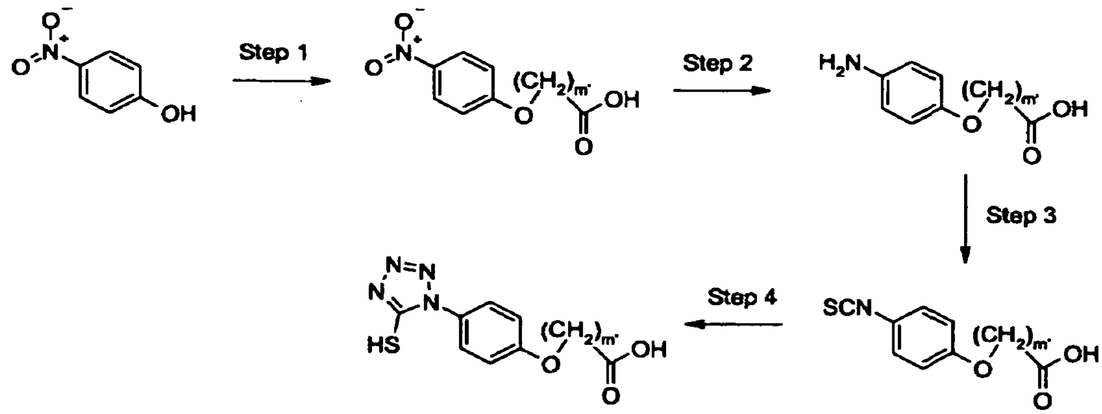


Example 731



Preparation of 1-aryl-1,4-dihydrotetrazole-5-thiones (or the tautomeric 1-aryltetrazole-5-thiols) is described in the literature (eg. by Kauer & Sheppard, *J. Org. Chem.*, **32**, 3580-92 (1967)) and is generally performed eg. by reaction of aryl-isothiocyanates with sodium azide followed by acidification

1-Aryl-1,4-dihydrotetrazole-5-thiones with a carboxylic acid tethered to the aryl group may be prepared as shown in the following scheme:



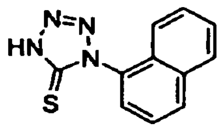
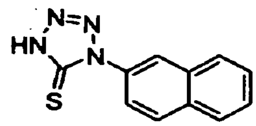
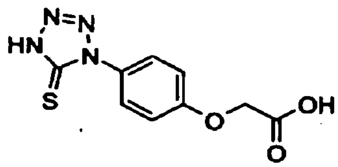
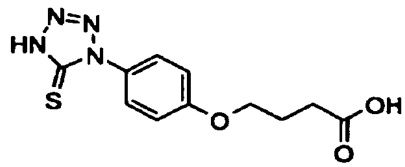
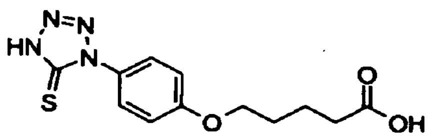
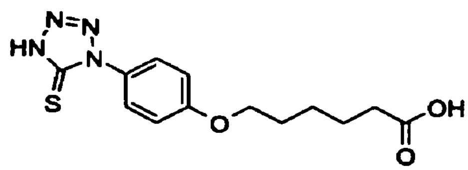
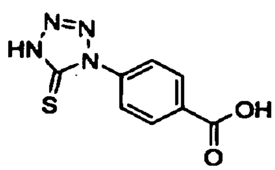
Step 1 is a phenol alkylation and is very similar to steps 1 and 2 of general procedure (D) and may also be prepared similarly as described in example 313.

Step 2 is a reduction of the nitro group. $SnCl_2$, H_2 over Pd/C and many other procedures known to those skilled in the art may be utilised.

Step 3 is formation of an arylisothiocyanate from the corresponding aniline. As reagents CS_2, $CSCl_2$, or other reagents known to those skilled in the art, may be utilised.

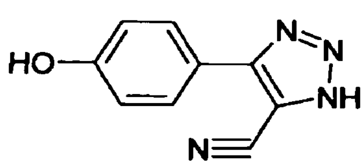
Step 4 is a conversion to mercaptotetrazole as described above.

Compounds of the invention includes:

Example 732 	**Example 733** 
Example 734 	**Example 735** 
Example 736 	**Example 737** 
Example 738 	

Example 739

4-(4-Hydroxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



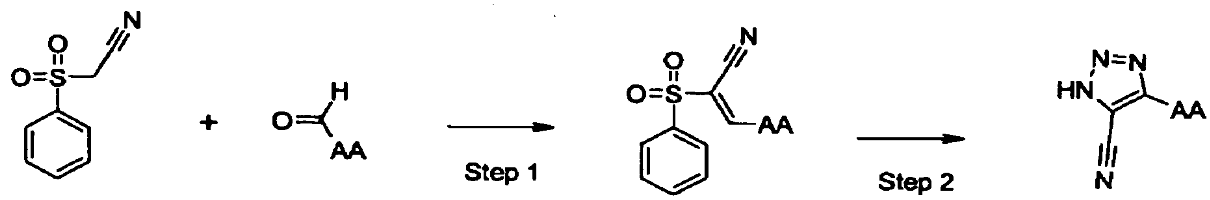
Phenylsulphonyl acetonitrile (2.0 g, 11.04 mmol) was mixed with 4-hydroxybenzaldehyde (1.35 g, 11.04 mmol) in DMF (10 mL) and toluene (20 mL). The mixture was refluxed for 3 hours and subsequently evaporated to dryness *in vacuo*. The residue was treated with

diethyl ether and toluene. The solid formed was filtered to afford 2.08 g (66%) of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile.
HPLC-MS (Method C): m/z: 286 (M+1); Rt. = 3.56 min.

A mixture of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile (2.08 g, 7.3 mmol) and sodium azide (0.47g,7.3 mmol) in DMF (50 mL) was heated at reflux temperature 2 hours. After cooling, the mixture was poured on ice. The mixture was evaporated in vacuo to almost dryness and toluene was added. After filtration, the organic phase was evaporated *in vacuo*. The residue was purified by silicagel chromatography eluting with a mixture of ethyl acetate and heptane (1:2). This afforded 1.2 g (76%) of the title compound.

1H NMR (DMSO-d_6): 10.2 (broad,1H); 7.74 (d,2H); 6.99 (d,2H); 3.6-3.2 (broad,1H).
HPLC-MS (Method C) m/z: = 187 (M+1); Rt. = 1.93 min

General procedure (O) for preparation of compounds of general formula I_{14}:



I_{14}

wherein
AA is as defined above,

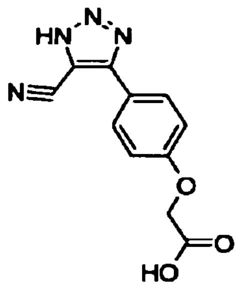
Steps 1 and 2 are described in the literature (eg Beck & Gûnther, *Chem. Ber.*, **106**, 2758-66 (1973))

Step 1 is a Knoevenagel condensation of the aldehyde AA-CHO with phenylsulfonyl-acetonitrile and step 2 is a reaction of the vinylsulfonyl compound obtained in step 1 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

This general procedure is further illustrated in the following example 740:

Example 740 (General Procedure (O))

[4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid

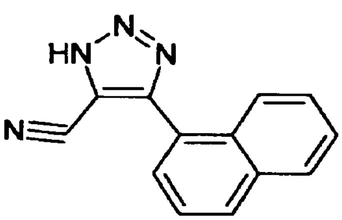


Phenylsulphonylacetonitrile (0.1 g, 0.55 mmol) was mixed with 4-formylphenoxyactic acid (0.099 g, 0.55 mmol) in DMF (3 mL) and heated to 110 °C for 3 h and subsequently cooled to RT. Sodium azide (0.036 g, 0.55 mmol) was added and the resulting mixture was heated to 110 °C for 3 h and cooled to RT. The mixture was poured into water (20 mL) and centrifuged. The supernatant was discarded, ethanol (5 mL) was added and the mixture was centrifuged again. After discarding the supernatant, the residue was dried *in vacuo* to afford 50 mg (37%) of [4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid.

HPLC-MS (Method C): m/z: 245 (M+1) Rt. 2.19 min.

Example 741 **(General Procedure (O))**

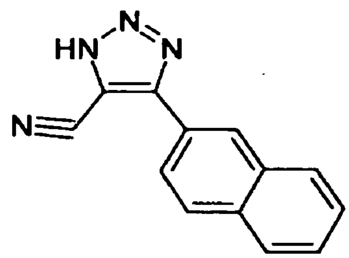
5-(Naphthalen-1-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 221 (M+1); Rt. 3.43 min.

Example 742 **(General Procedure (O))**

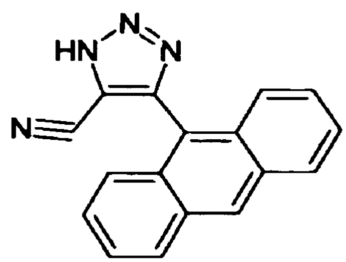
5-(Naphthalen-2-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 221 (M+1); Rt = 3.66 min.

Example 743 **(General Procedure (O))**

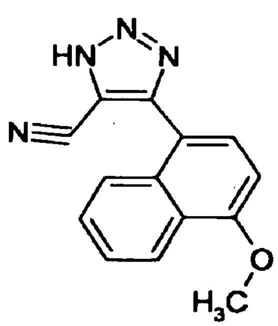
5-(Anthracen-9-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 271 (M+1); Rt = 3.87 min.

Example 744 **(General Procedure (O))**

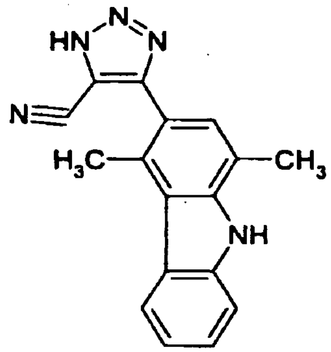
5-(4-Methoxynaphthalen-1-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 251 (M+1); Rt = 3.57 min.

Example 745 **(General Procedure (O))**

5-(1,4-Dimethyl-9*H*-carbazol-3-yl)-3*H*-[1,2,3]triazole-4-carbonitrile

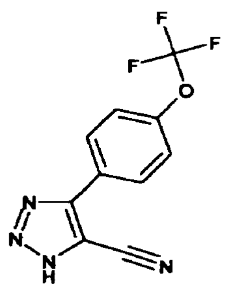


HPLC-MS (Method C): m/z: 288 (M+1); Rt = 3.67 min.

The compounds in the following examples are commercially available and may be prepared using a similar methodology:

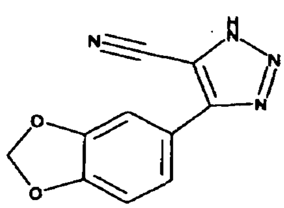
Example 746

4-(4-Trifluoromethoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



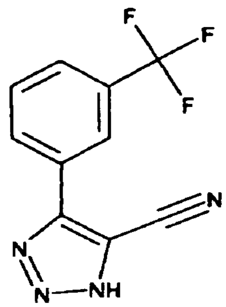
Example 747

4-Benzo[1,3]dioxol-5-yl-1*H*-[1,2,3]triazole-5-carbonitrile



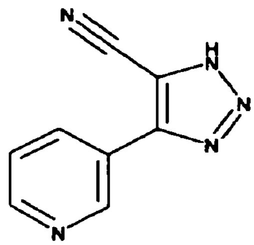
Example 748

4-(3-Trifluoromethylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



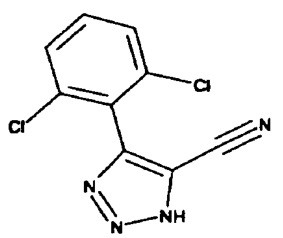
Example 749

4-Pyridin-3-yl-1*H*-[1,2,3]triazole-5-carbonitrile



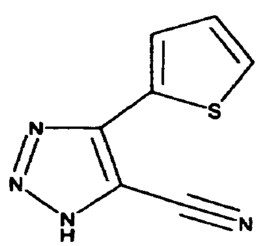
Example 750

4-(2,6-Dichlorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



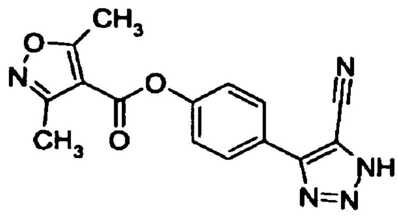
Example 751

4-Thiophen-2-yl-1*H*-[1,2,3]triazole-5-carbonitrile



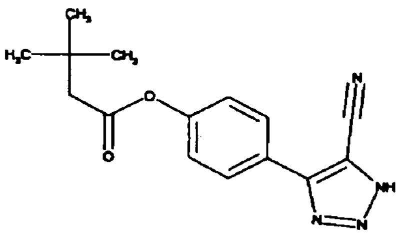
Example 752

3,5-Dimethylisoxazole-4-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



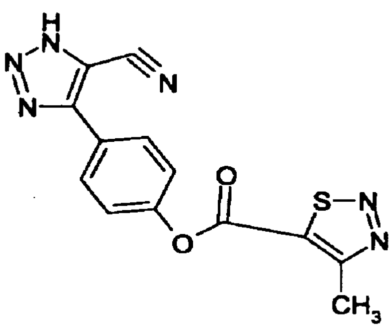
Example 753

3,3-Dimethyl-butyric acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



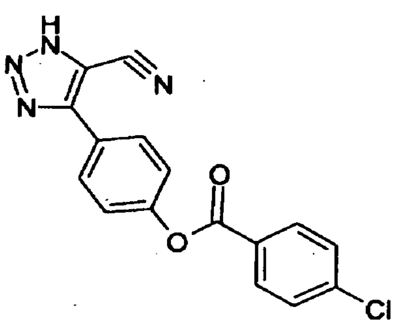
Example 754

4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



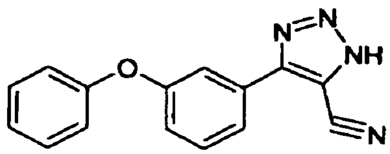
Example 755

4-Chlorobenzoic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester



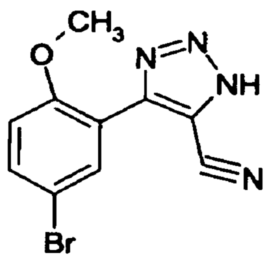
Example 756

4-(3-Phenoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



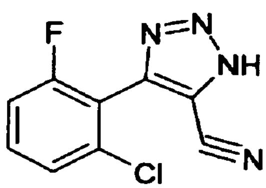
Example 757

4-(5-Bromo-2-methoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



Example 758

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

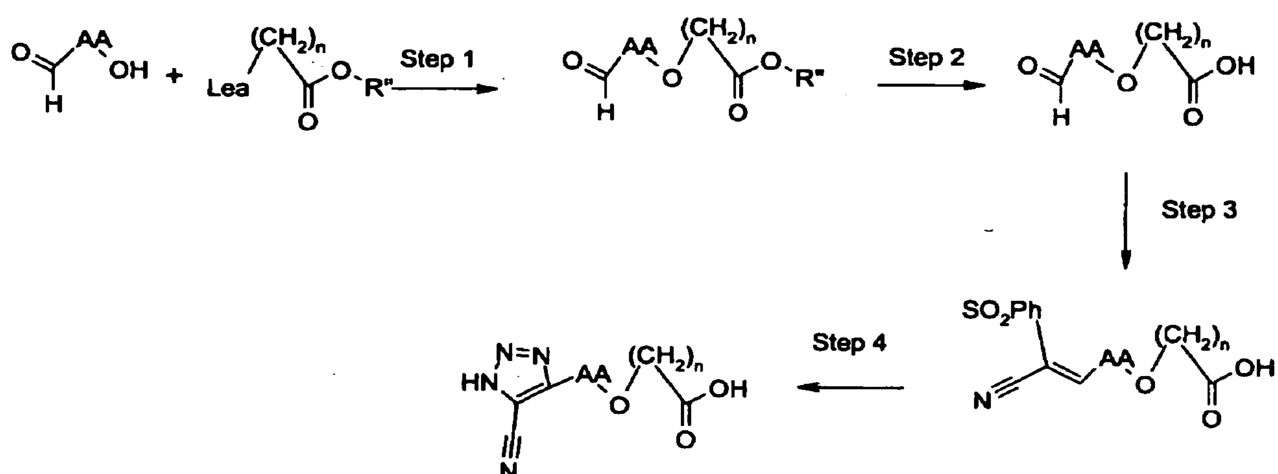


The following cyanotriazoles are also compounds of the invention:

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
Terephthalic acid mono[4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl] ester.
N- [4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)-phenyl]terephthalamic acid
4-(4-Octyloxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile
4-(4-Styrylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(4'-Trifluoromethylbiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(4'-Chlorobiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(4'-Methoxybiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(1-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

4-(9-Anthranyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(4-Methoxy-1-naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(4-Aminophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
4-(2-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

General procedure (P) for preparation of compounds of general formula I_{15}:



I_{15}

wherein
n is 1 or 3-20,
AA is as defined above,
R" is a standard carboxylic acid protecting group, such as C_1-C_6-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the like.

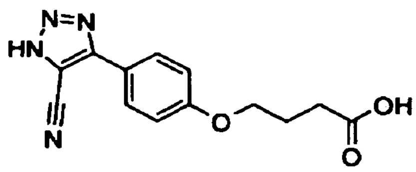
This procedure is very similar to general procedure (D), steps 1 and 2 are identical.

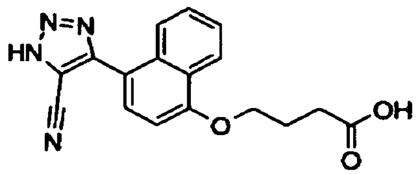
Steps 3 and 4 are described in the literature (eg Beck & Gûnther, *Chem. Ber.*, **106**, 2758-66 (1973))

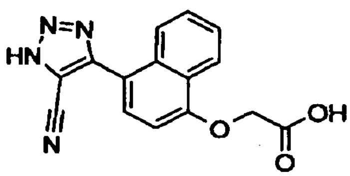
Step 3 is a Knoevenagel condensation of the aldehyde obtained in step 2 with phenylsulfonylacetonitrile and step 4 is a reaction of the vinylsulfonyl compound obtained in step 3 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

The following compounds may be prepared according to this general procedure (P):

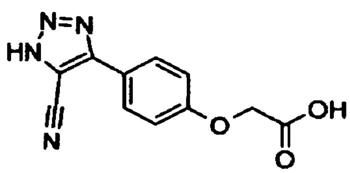
4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid:







2-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)acetic acid:



4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid ethyl ester

5-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)pentanoic acid

8-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)octanoic acid

10-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)decanoic acid

12-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)dodecanoic acid

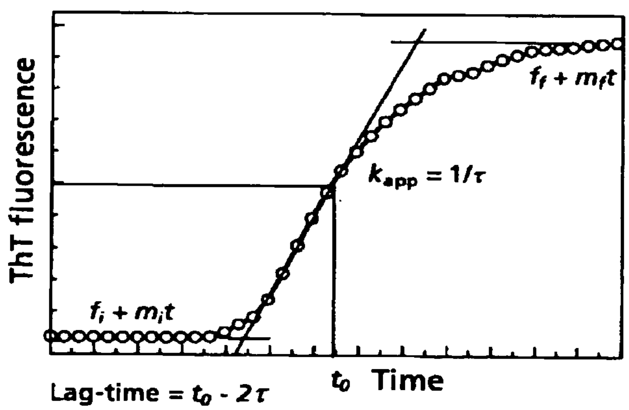
Example 759 Characterization of ligand effects on physical stability of formulations by the Thioflavine T fluorescence assay.

Low physical stability of insulin formulations may lead to amyloid fibril formation, which is observed as well-ordered, thread-like macromolecular structures in the sample eventually resulting in gel formation. This has traditionally been measured by visual inspection of the

sample. However, the application of a small molecule indicator probe is much more preferable. Thioflavin T is such a probe and has a distinct fluorescence signature when binding to fibrils (or rather β-sheet rich proteins) [Naiki et al. (1989) Anal. Biochem. **177**, 244-249; LeVine (1999) Methods. Enzymol. **309**, 274-284]. Its application to insulin fibrillation has recently been validated [Nielsen et al. (2001) Biochemistry **40**, 6036-6046].
The time course for fibril formation can be described by a sigmoidal curve with the following expression:

$$F = f_i + m_i t + \frac{f_f + m_f t}{1 + e^{-[(t-t_0)/\tau]}} \quad \text{Eq.(1)}$$

Here, F is the ThT fluorescence at the time t. The constant t_0 is the time needed to reach 50% of maximum fluorescence. The minimum and maximum fluorescence is denoted f_i and f_f, respectively, and the expressions $m_i t$ and $m_f t$ describe the linear development of the bottom and top base lines. The two important parameters describing fibril formation are the lag-time calculated by $t_0 - 2\tau$ and the apparent rate constant $k_{app} = 1/\tau$.



Formation of a partially folded intermediate of the protein is suggested as a general initiating mechanism for fibrillation. Few of those intermediates nucleate to form a template onto which further intermediates may assembly and the fibrillation is initiated. The lag-time corresponds to the interval in which the critical mass of nucleus is built up and the apparent rate constant is the rate with which the fibril itself is formed.

In accordance with this mechanism, insulin needs to dissociate to its monomeric form before a partially folded intermediate may be formed. Keeping insulin on a multimeric form may therefore result in increased physical stability. Ligands binding to the insulin hexamer zinc site should stabilize the hexameric form and draw the equilibrium even further away from the monomeric form. Hence, an increased physical stability could be achieved.

Sample preparation

Insulin formulations were prepared freshly before each assay from appropriate stock solutions. Typical final concentrations were 0.6 mM human insulin or insulin aspart analogue, 0.2 mM ZnAc, 30 mM phenol, 10 mM Tris pH 8. ThT was added from a 1 mM stock solution in water to a final concentration of 1 μM. The formulations were typically prepared in double concentration and mixed with an equal volume of test compound in appropriate concentration in 4% DMSO, 10 mM Tris pH 8.

Alternatively, insulin aspart formulations (100 U/ml) from the production line were used directly. ThT was added to 1 μM and DMSO containing test compound in appropriate concentration to 2%.

Sample aliquots of 200 μl were placed in a 96 well microtiter plate (Packard OptiPlate™-96, white polystyrene). Usually, eight replica of each sample (corresponding to one test compound concentration) was placed in one column of wells. The plate was sealed with Scotch Pad (Qiagen).

Control experiments for possible test compound quenching of the ThT emission were carried out using human insulin without Zn^{2+} and phenol i.e. in a non-hexameric configuration. Hence, the fibrillation process as well as the ThT emission should be unaffected by the presence of test compound, unless it quenched the ThT signal.

Incubation and fluorescence measurement

Temperature incubation, shaking and measurement of the ThT fluorescence were done in a Fluoroskan Ascent FL fluorescence platereader (Thermo Labsystems). Temperature setting is possible up till 45 °C, but usually sat at 30 °C. Heating was initiated at first measurement. The orbital shaking is selectable up till 1200 rpm, but adjusted to 960 rpm in all the presented data with an amplitude of 1 mm.

Fluorescence measurement was done using excitation trough a 444 nm filter and measurement of emission through a 485 nm filter. Each run was initiated by a measurement and intervals between measurements were usually 20 min. The plate was shaken and heated as adjusted between each measurement. The assay time was regulated by the

number of measurements and the interval in between. Usually the plate was measured 46 times with 20 min between, i.e. over 15 hours.

Data handling

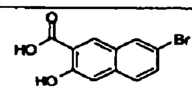
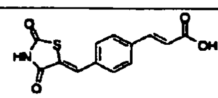
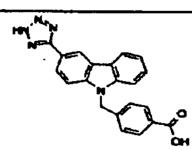
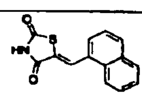
The measurement points were saved in Microsoft Excel format for further processing and curve drawing and fitting was performed using GraphPad Prism. The background emission from ThT in the absence of fibrils was negligible. Some test compounds had background fluorescence under the applied experimental conditions. This was eliminated by subtracting the mean value of the first measurement from the data set for this test compound. The data points are shown with standard deviation.

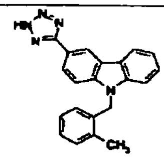
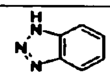
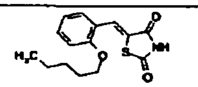
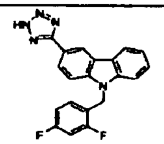
The data set may be fitted to Eq. (1). However, since the stabilizing effect of the test compounds/ligands were so significant that a full sigmoid curve was not obtained during the usual assay time, curve fitting to such a data set would be imprecise and hence meaningless.

Only data obtained in the same experiment (i.e. samples on the same plate) are presented in the same graph.

Examples & Results

The various ligands are shown below with structure and affinity towards the zinc site as measured by the TZD-assay described in "Analytical Methods".

Reference	Example	Compound	K_d(app) (nM)
A	376		383
C	294		58
D	581		171
E	61		23

F	599		3
G	1		3879
H	68		82
I	602		23

The ThT assays of various combinations of insulin formulations and ligands are shown in Fig. 1 – 8.

Addition of ligands improves the physical stability of insulin formulations. This holds for human insulin formulations (see Fig 1) as well as insulin aspart formulations (rest of data set).

The improved stability can be obtained by using various compound classes as zinc site anchor, e.g. benzothriazoles (G, Fig 1), naphthosalicylic acids (A, Fig 2), thiazolidine-diones (E, Figs 4, 7; C, Fig 2; H, Figs 6, 8) and tetrazoles (D, Fig 3; F, Fig 8; I, Fig 5).

Increased affinity of the ligand results in higher stability of the formulation. Compare the effect of the weakest binding ligand in 2 mM (G, Fig. 1) with the effect on an insulin aspart formulation of 0,5 mM E (Fig. 4). Also compare the effects of similar concentrations of A and C (Fig 2); and of D (fig. 3) and E (Fig 4) on insulin aspart formulations.

Increasing the concentration of ligand tends to improve the stabilization (see Figs. 1, 3, 4, 5, 6). In some instants, more pronounced effects are seen with the ligand in slight molar excess to the zinc sites, see Figs. 4, 6, whereas it seems to plateau around the stoichiometric concentration in other instances (Figs. 3, 5).

Of the presented ligands, A, C, D, E, F were tested in a disappearance assay for the effect on release of insulin aspart from a subcutaneous inject site. Surprisingly, the ligands had no effect on the insulin aspart disappearance. In a very limited way, this can be mimicked in the ThT assay by increasing the assay temperature to 37 °C (see Figs. 7, 8). The stabilizing

effect is somewhat attenuated, e.g. compare E at 30 °C (Fig 4) and 37 °C (Fig 7), and H (Fig 6 and 8). The ligand with highest affinity (F) has the most stabilizing effect at 37 °C (Fig. 8).

Fig 1

0,6 mM HI, 0,2 mM Zn^{2+}, 30 mM phenol, 1 µM ThT, pH 7,5, 30 °C, 960 rpm

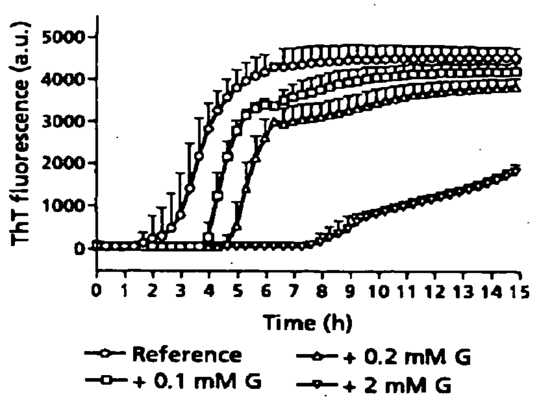


Fig 2

Aspart formulation, 1 µM ThT, 30 °C, 960 rpm

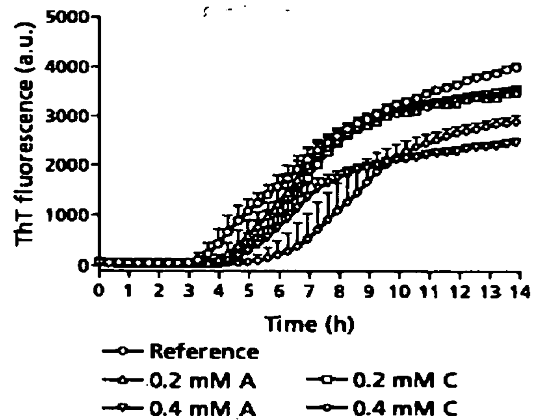


Fig 3

Aspart Formulation, 1 µM ThT, 30 °C, 960 rpm.

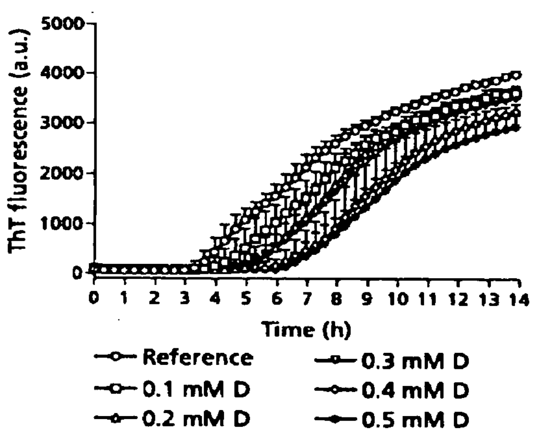


Fig 4

Aspart formulation, 1 µM ThT, 30 °C, 960 rpm.

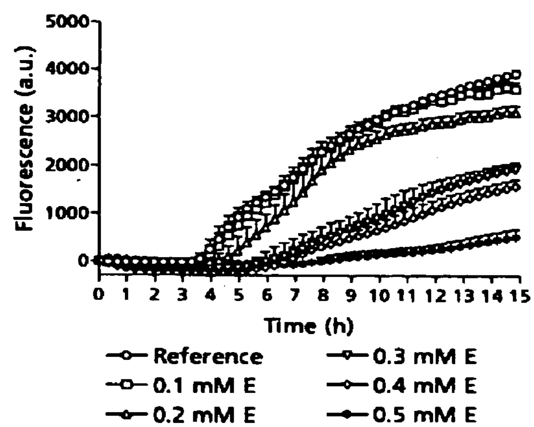


Fig 5

Aspart formulation, 1 µM ThT, pH 8, 30 °C, 960 rpm.

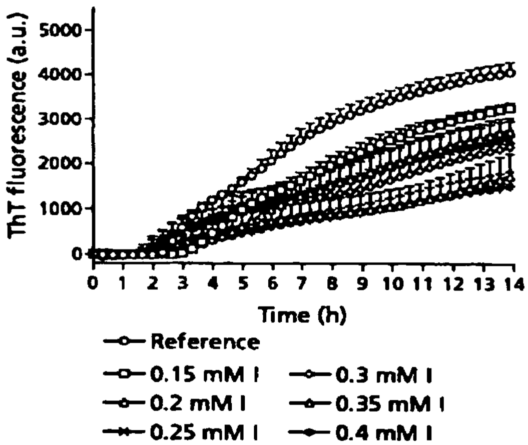


Fig 6

Aspart formulation, 1 µM ThT, pH 8, 30 °C, 960 rpm.

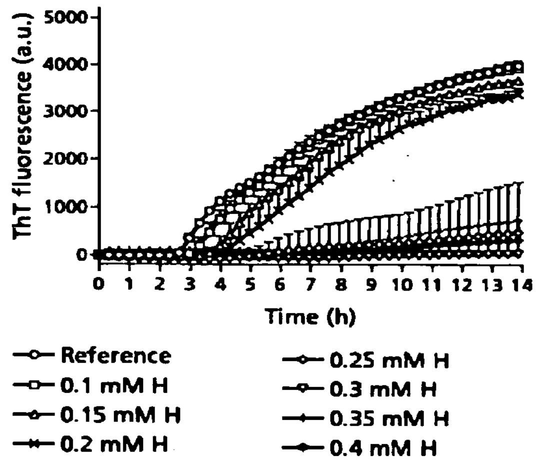


Fig 7

Aspart formulation , 1 µM ThT, 37 °C, 960 rpm

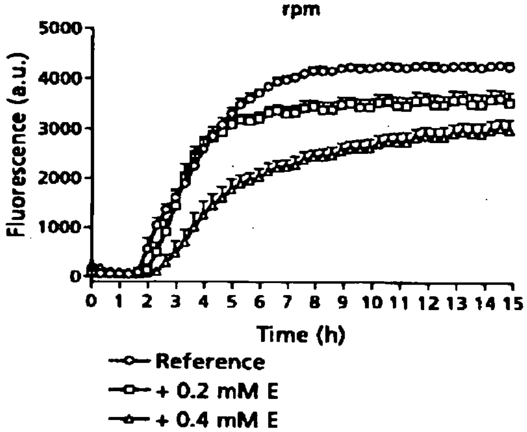
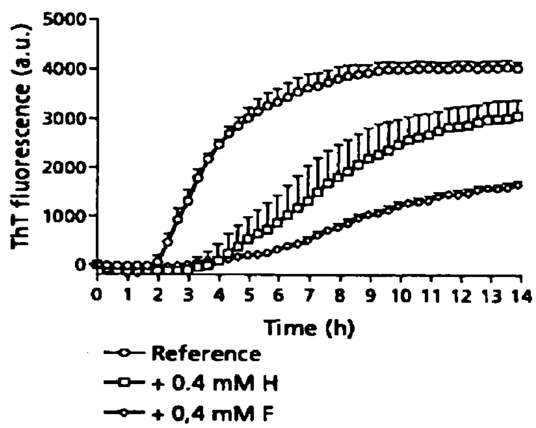


Fig 8

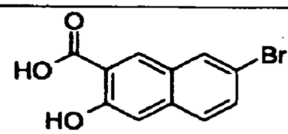
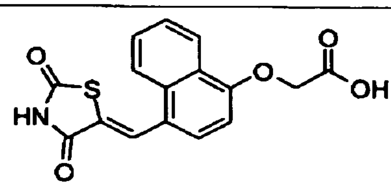
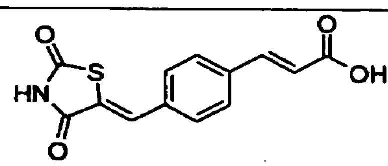
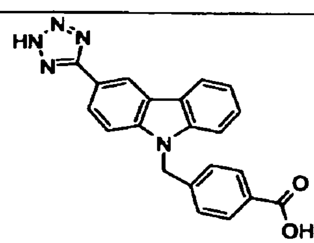
Aspart formulation, 1 µM ThT, 37 °C, 960 rpm.

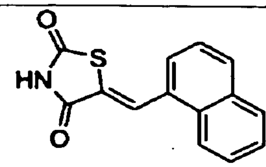
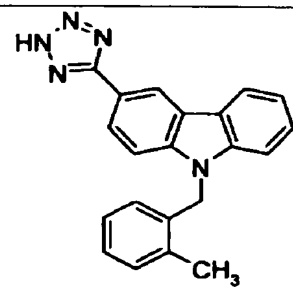


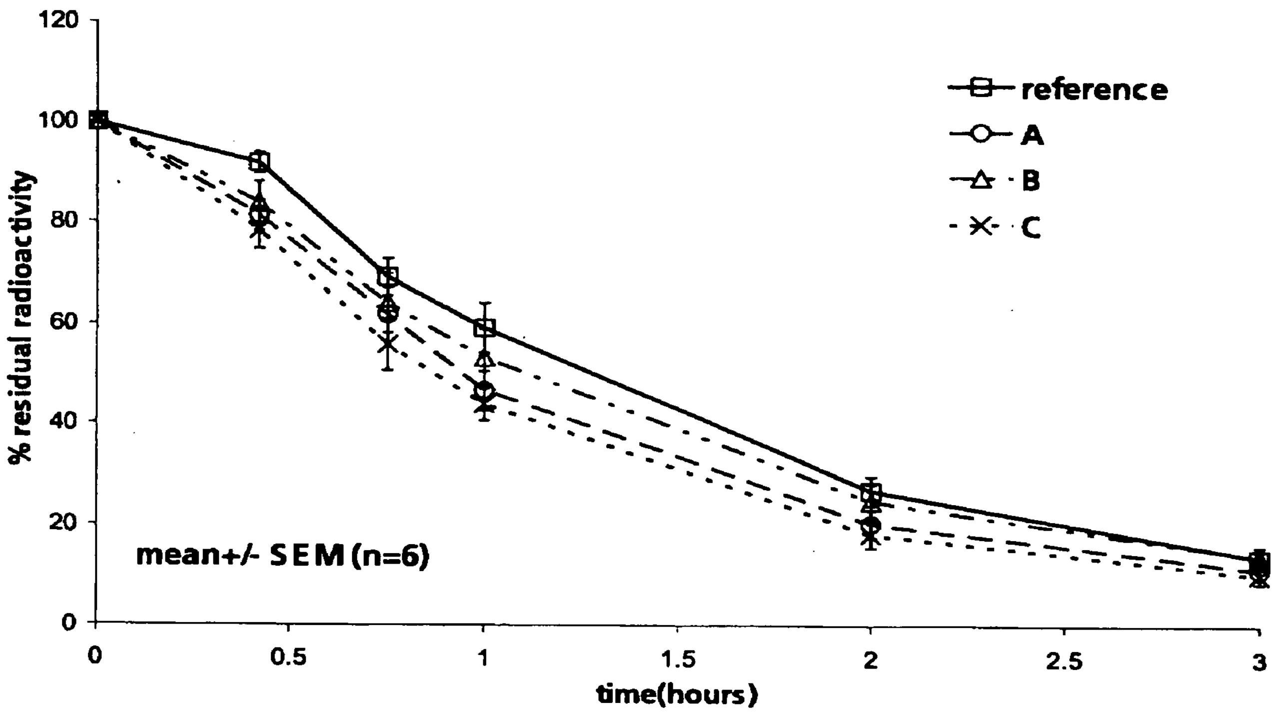
Example 760 Retention of fast absorption characteristics of formulations stabilized by addition of His^{B10} Zn^{2+}-site ligands.

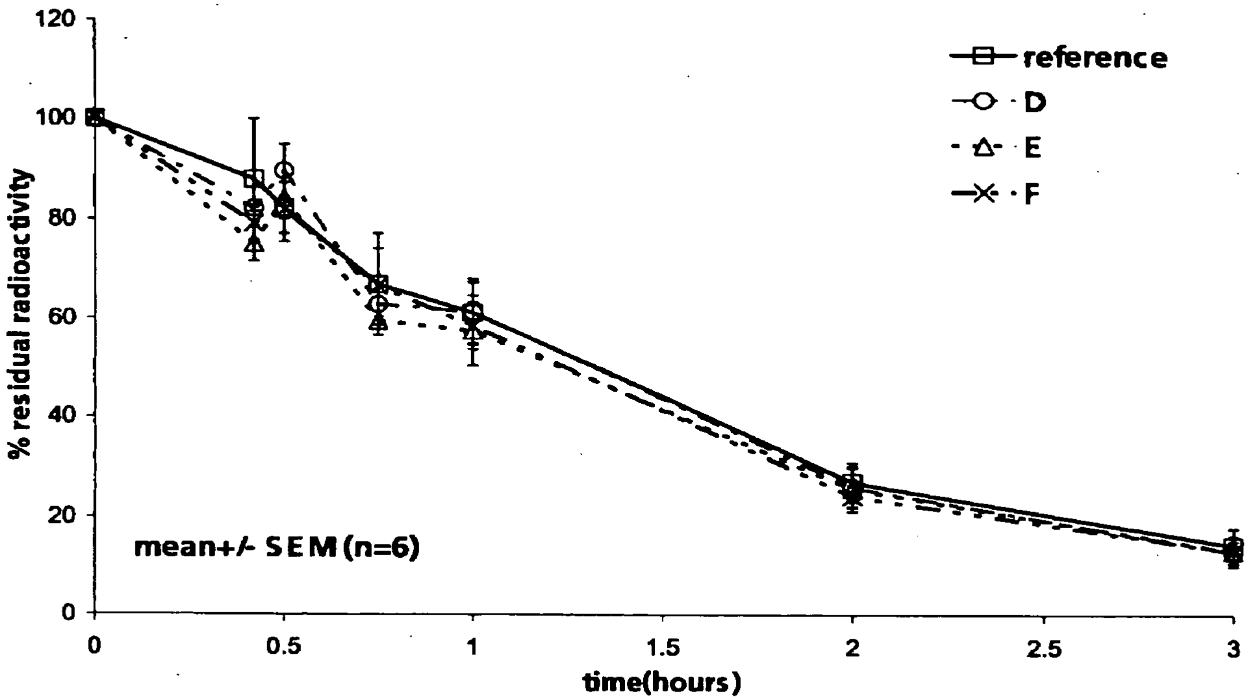
Formulations of the present invention were characterized by the disappearance rate from the subcutaneous depot following injection in pigs. Formulations of B28 Asp human insulin containing A14Tyr(^{125}I) B28 Asp human insulin were followed with an external γ-counter

(Ribel et al., The pig as a model for subcutaneous absorption in man. In: Serrano-Ritos & Lefebre (Eds.): Diabetes (1985) proceedings ot the 12[th] congress of the international diabetes federation, Madrid, Spain, 1985 (Excerpta Medica, Amsterdam (1986) 891-896. Formulations of Insulin Aspart (0.6 mM, U100) containing 0.3 mM Zn^{2+}, 30 mM phenol, 2 mM phosphate buffer, and 1.6% glycerol, pH 7.4, were compared with the corresponding formulations containing 0.3 mM of the ligands shown below: where $T_{50\%}$ is the time when 50% ot the A14Tyr(^{125}I) B28 Asp insulin has disappeared from the site of injection and K_d is the affinity of the ligand as measured by the TZD-assay described in "Analytical methods" below. It is evident that the stabilizing ligands do not affect the fast absorption properties of the formulations

	Example #	Compound	T50%	K_d (app) (nM)
reference			1.3± 0.3	
A	376		1.0± 0.23	383
B	308		1.1± 0.37	68
C	294		0.9± 0.19	58
D	581		1.3± 0.36	171

E	61		1.2± 0.41	23
F	599		1.2± 0.27	3





Example 761

Reference experiment

The chemical stability of insulin formulations of the invention was characterised by HPLC (RPC, reverse phase chromatography and SEC, size exclusion chromatography). As reference, insulin formulated without ligands of the invention but with 0.3 % DMSO was also investigated and shown below:

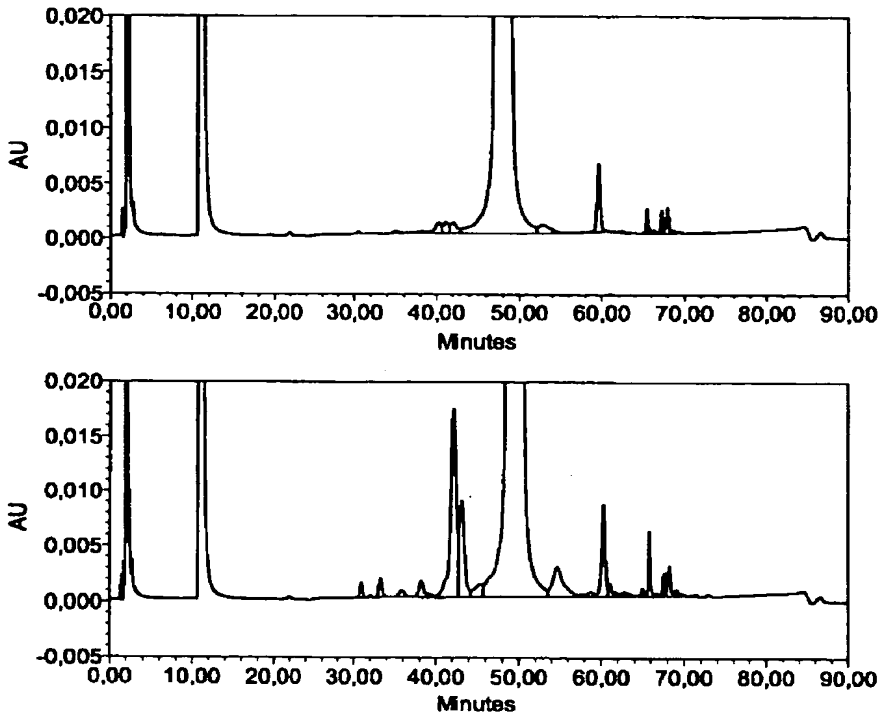


Figure 9

Fig 1. Reverse phase chromatography of formulated human insulin with 3 Zn^{2+} per hexamer, 30 mM phenol, 150 mM mannitol, 3 mM phosphoric acid, sodium hydroxide to pH 7.4 and 0.3 % DMSO corresponding to 3 ligands per hexamer at start (upper panel) and after storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

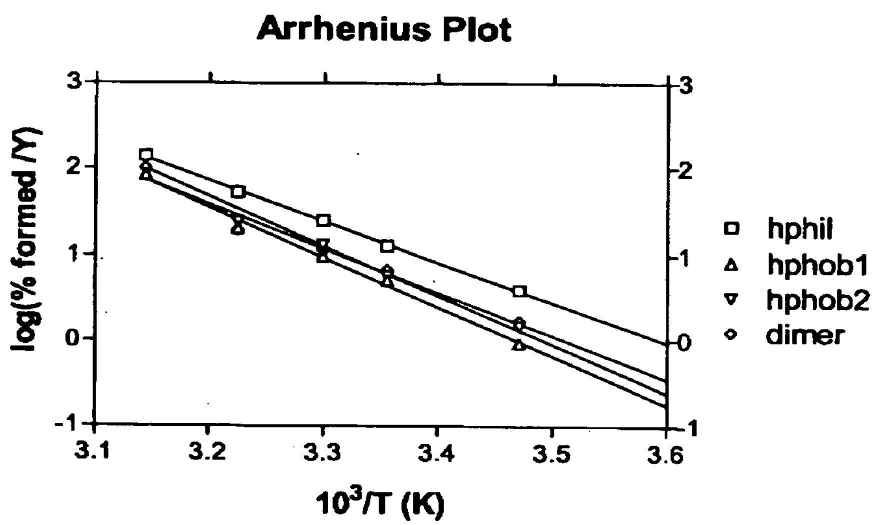
Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) gave about the same increase of transformation products correlating to an increase in reactions constants of a factor 3-4 per 10 degree..

RPC (reverse phase chromatography) on Waters SymmetryShield RP_8 column, 150×4.6 mm and 3.5 µm, eluted by **A:** 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 %

acetonitrile and isocratically (i) or a gradient (g) of B: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile: arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	153.3	47.5	23.4	21.9
37°C	57.2	15.6	5.20	6.24
30°C	24.5	4.16	1.30	2.08
25°C	14.2	2.13	0.68	1.09
15°C	4.12	0.43	0.22	0.31
5°predicted	(1.001)	(0.066)	(0.027)	(0.052)



The chemical stability of insulin formulations of the invention were likewise characterised by HPLC (RPC, reverse phase chromatography and SEC, size exclusion chromatography). Compared to the reference the formulations of the invention were shown to be more chemically stable.

Example 762

Chemical stability of insulin formulated with the compound of example 376 , 7-bromo-3-hydroxy-2-naphthoic acid:

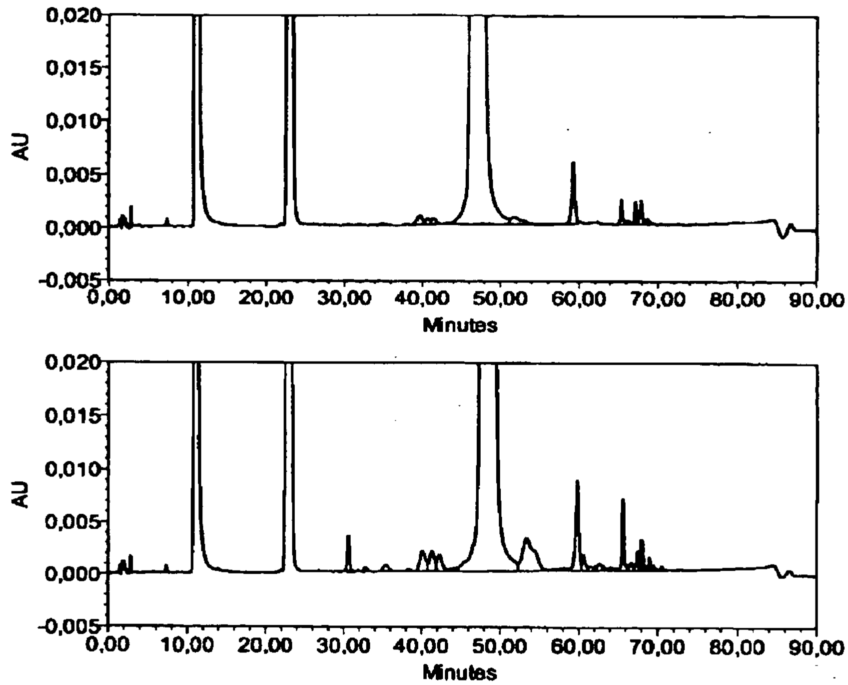


Figure 10

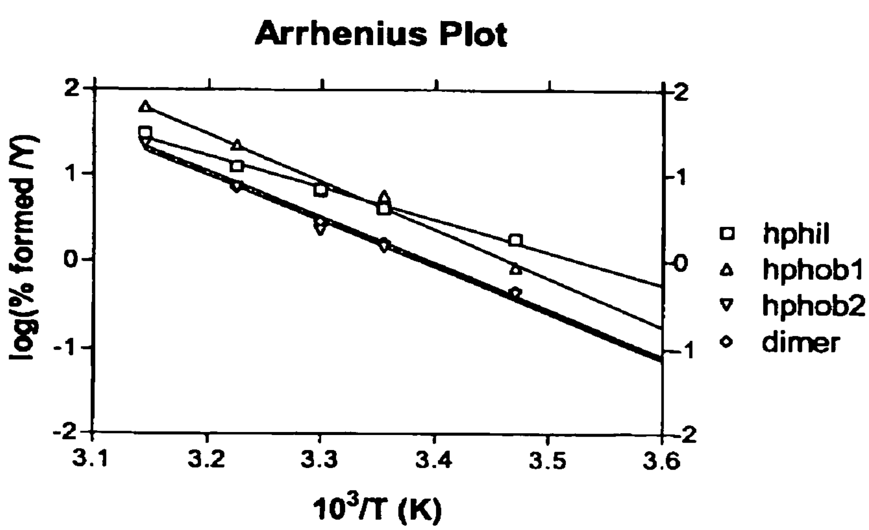
Fig 2. Reverse phase chromatography of formulated human insulin as described for the reference example and added 3 ligands of Example 376 and 3 Zn^{2+} per hexamer at start (upper panel) and after storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) will give about the same increase in transformation products correlating to an increase in reaction constants of a factor 3-4 per 10 degrees...

RPC (reverse phase chromatography) on Waters SymmetryShield RP_8 column, 150×4.6 mm and 3.5 µm, eluted by **A:** 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of **B:** 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	30.7	62.1	23.4	26.3
37°C	12.5	22.4	7.02	7.02
30°C	6.76	6.42	2.25	2.86
25°C	4.06	5.67	1.46	1.61
15°C	1.80	0.85	0.42	0.45
5°predicted	(0.55)	(0.19)	(0.079)	(0.087)



Example 763

Chemical stability of insulin formulated with the compound of Example 294, 3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]acrylic acid:

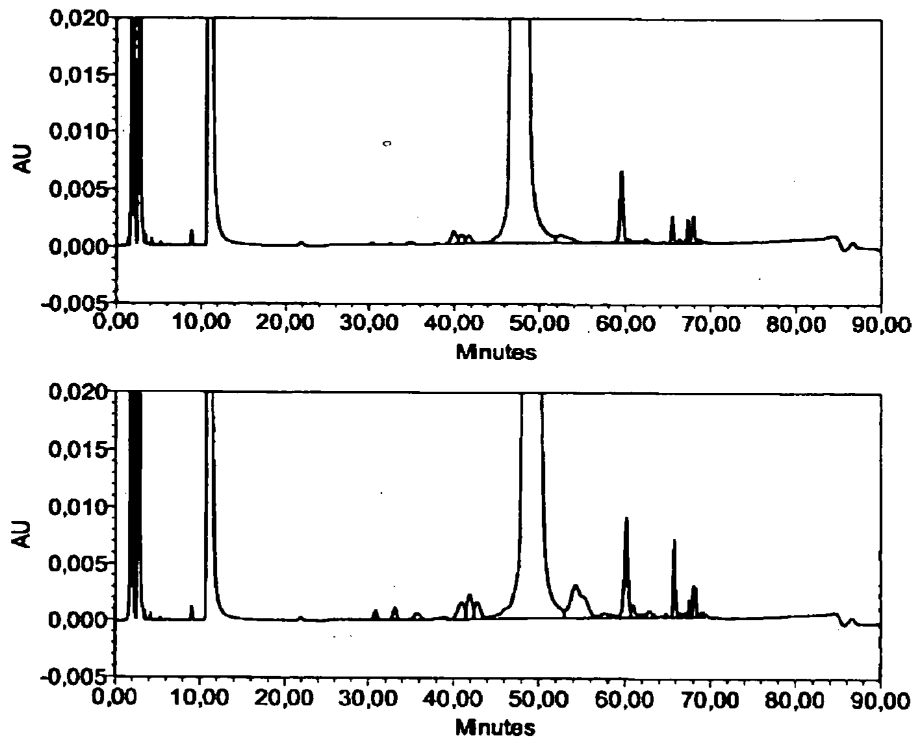


Figure 11

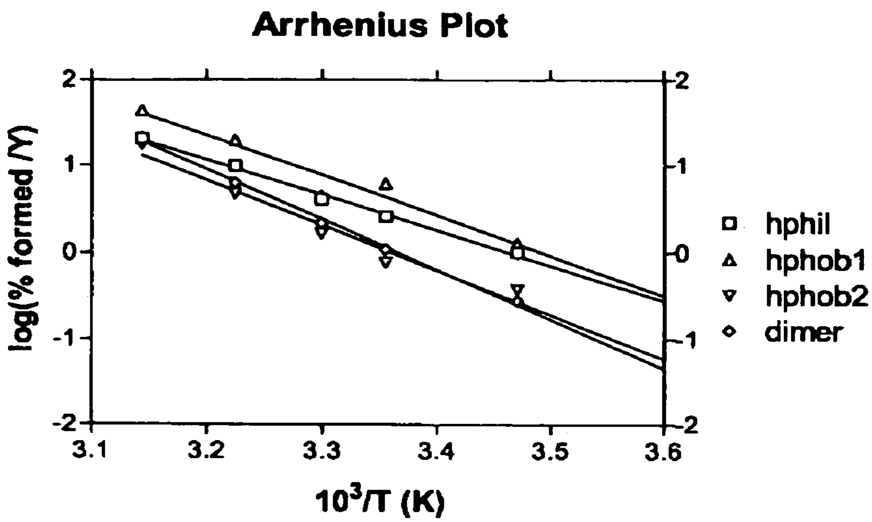
Fig 3. Reverse phase chromatography of formulated human insulin as described for the reference example and added 3 ligands of example 294 and 3 Zn^{2+} per hexamer at start (upper panel) and after storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) will give about the same increase in transformation products correlating to an increase in reaction constants of a factor 3-4 per 10 degrees.

RPC (reverse phase chromatography) on Waters SymmetryShield RP_8 column, 150×4.6 mm and 3.5 μm, eluted by **A:** 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of **B:** 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	**RPC**			**SEC**
	hphil	hphob1	hphob2	Dimer
45°C	20.4	43.8	17.5	21.2
37°C	9.88	19.5	4.68	6.24
30°C	4.07	4.42	1.65	2.17
25°C	2.60	6.14	0.78	1.09
15°C	1.02	1.28	0.38	0.28
5°predicted	(0.293)	(0.336)	(0.062)	(0.048)


Arrhenius Plot
log(% formed /Y)
10^3/T (K)
hphil
hphob1
hphob2
dimer
2
1
0
-1
-2
3.1
3.2
3.3
3.4
3.5
3.6

ANALYTICAL METHODS

Assays to quantify the binding affinity of ligands to the metal site of the insulin R_6 hexamers:

4H3N-assay:

The binding affinity of ligands to the metal site of insulin R_6 hexamers are measured in a UV/vis based displacement assay. The UV/vis spectrum of 3-hydroxy-4-nitro benzoic acid (4H3N) which is a known ligand for the metal site of insulin R_6 shows a shift in absorption maximum upon displacement from the metal site to the solution (Huang et al., 1997, Biochemistry 36, 9878-9888). Titration of a ligand to a solution of insulin R_6 hexamers with 4H3N mounted in the metal site allows the binding affinity of these ligands to be determined following the reduction of absorption at 444 nm.

A stock solution with the following composition 0.2 mM human insulin, 0.067 mM Zn-acetate, 40 mM phenol, 0.101 mM 4H3N is prepared in a 10mL quantum as described below. Buffer is always 50mM tris buffer adjusted to pH=8.0 with NaOH/ClO_4^-.

1000 µL of 2.0mM human insulin in buffer
66.7 µL of 10mM Zn-acetate in buffer
800 µL of 500mM phenol in H_2O
201 µL of 4H3N in H_2O
7.93 ml buffer

The ligand is dissolved in DMSO to a concentration of 20 mM.
The ligand solution is titrated to a cuvette containing 2 mL stock solution and after each addition the UV/vis spectrum is measured. The titration points are listed in Table 3 below.

Table 3

ligand addition (µl)	ligand conc. (mM)	dilution factor
1	0.010	1.0005
1	0.020	1.0010
1	0.030	1.0015
2	0.050	1.0025
5	0.100	1.0050
10	0.198	1.0100
20	0.392	1.0200
20	0.583	1.0300
20	0.769	1.0400
20	0.952	1.0500

The UV/vis spectra resulting from a titration of the compound 3-hydroxy-2-naphthoic acid is shown in Figure 5. Inserted in the upper right corner is the absorbance at 444nm vs. the concentration of ligand.
The following equation is fitted to these datapoints to determine the two parameters K_D(obs), the observed dissociation constant, and abs_{max} the absorbance at maximal ligand concentration.

$$abs([ligand]_{free}) = (abs_{max} * [ligand]_{free}) / (K_D(obs) + [ligand]_{free})$$

The observed dissociation constant is recalculated to obtain the apparent dissociation constant

$$K_D(app) = K_D(obs) / (1+[4H3N]/K_{4H3N})$$

The value of K_{4H3N}=50 μM is taken from Huang et al., 1997, Biochemistry 36, 9878-9888.

TZD-assay:

The binding affinity of ligands to the metal site of insulin R_6 hexamers are measured in a fluorescense based displacement assay. The fluorescence of 5-(4-dimethylaminobenzylidene)thiazolidine-2,4-dione (TZD) which is a ligand for the metal site of insulin R_6 is quenched upon displacement from the metal site to the solution. Titration of a ligand to a stock solution of insulin R_6 hexamers with this compound mounted in the metal

site allows the binding affinity of these ligands to be determined measuring the fluorescence at 455nm upon excitation at 410nm.

Preparation

Stock solution: 0.02 mM human insulin, 0.007 mM Zn-acetate, 40 mM phenol, 0.01 mM TZD in 50mM tris buffer adjusted to pH=8.0 with $NaOH/ClO_4^-$.

The ligand is dissolved in DMSO to a concentration of 5 mM and added in aliquots to the stock solution to final concentrations of 0-250 □M.

Measurements

Fluorescence measurements were carried out on a Perkin Elmer Spectrofluorometer LS50B.The main absorption band was excited at 410 nm and emission was detected at 455 nm. The resolution was 10 nm and 2.5 nm for excitation and emission, respectively.

Data analysis

This equation is fitted to the datapoints

$\Delta F(455nm)) = \Delta F_{max} * [ligand]_{free}/(K_D(app) * (1+[TZD]/K_{TZD})+ [ligand]_{free}))$

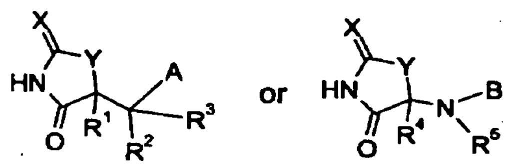
K_D(app) is the apparent dissociation constant and F_{max} is the fluorescence at maximal ligand concentration. The value of K_{TZD} is measured separately to 230 nM

Two different fitting-procedures can be used. One in which both parameters, K_D(app) and F_{max}, are adjusted to best fit the data and a second in which the value of F_{max} is fixed (F_{max}=1) and only K_D(app) is adjusted. The given data are from the second fitting procedure. The Solver module of Microsoft Excel can be used to generate the fits from the data points.

CLAIMS

1. A pharmaceutical composition comprising insulin and a zinc-binding ligand which reversibly binds to a His^{B10} Zn^{2+} site of an insulin hexamer, wherein the ligand is selected from the group consisting of benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

2. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is



wherein

X is =O, =S or =NH

Y is -S-, -O- or -NH-

R^1 and R^4 are independently selected from hydrogen or C_1-C_6-alkyl,

R^2 is hydrogen or C_1-C_6-alkyl or aryl, R^1 and R^2 may optionally be combined to form a double bond,

R^3 and R^5 are independently selected from hydrogen, halogen, aryl, C_1-C_6-alkyl, or -C(O)$NR^{11}R^{12}$,

A and B are independently selected from C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^6 and the aryl or heteroaryl is optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10},

A and R^3 may be connected through one or two valence bonds, B and R^5 may be connected through one or two valence bonds,

R^6 is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, aryl, -COOH and $-NH_2$,

R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$,

$-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2$ R^{11}, $-C(O)NR^{11}R^{12}$, $-OC(O)NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-CH_2C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_{15}-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-NR^{11}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{11}$, $-NR^{11}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, $C(O)R^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$, =O, or $-C_2$-C_6-alkenyl-$C(=O)$-$NR^{11}R^{12}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents independently selected from R^{13},

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl, or C_3-C_6 cycloalkyl,

of which each cyclic moiety may optionally be substituted with one or more substituents independently selected from R^{14},

R^{11} and R^{12} are independently selected from hydrogen, OH, C_1-C_{20}-alkyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{13} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{11}$, $-C(O)OR^{11}$, $-NR^{11}R^{12}$, and $-C(O)NR^{11}R^{12}$,

R^{14} is independently selected from halogen, $-C(O)OR^{11}$, $-CH_2C(O)OR^{11}$, $-CH_2OR^{11}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $S(O)_2R^{11}$, aryl and C_1-C_6-alkyl,

R^{15} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, -COOH and $-NH_2$,

R^{16} is independently selected from halogen, -C(O)OC$_1$-C$_6$-alkyl, -COOH, -CN, -CF$_3$, -OCF$_3$, -NO$_2$, -OH, -OC$_1$-C$_6$-alkyl, -NH$_2$, C(=O) or C$_1$-C$_6$-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

3. A pharmaceutical composition according to claim 2 wherein X is =O or =S.

4. A pharmaceutical composition according to claim 3 wherein X is =O.

5. A pharmaceutical composition according to claim 3 wherein X is =S.

6. A pharmaceutical composition according to any one of the claims 2 to 5 wherein Y is -O- or -S-.

7. A pharmaceutical composition according to claim 6 wherein Y is -O-.

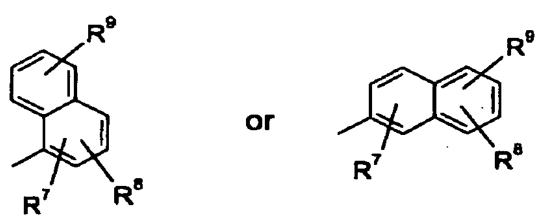
8. A pharmaceutical composition according to claim 6 wherein Y is -S-.

9. A pharmaceutical composition according to any one of the claims 2 to 8 wherein A is aryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

10. A pharmaceutical composition according to claim 9 wherein A is selected from ArG1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

11. A pharmaceutical composition according to claim 10 wherein A is phenyl or naphtyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

12. A pharmaceutical composition according to claim 11 wherein A is



13. A pharmaceutical composition according to claim 11 wherein A is phenyl.

14. A pharmaceutical composition according to any one of the claims 2 to 8 wherein A is heteroaryl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

15. A pharmaceutical composition according to claim 14 wherein A is selected from Het1 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

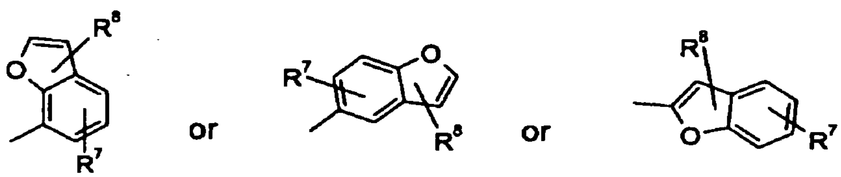
16. A pharmaceutical composition according to claim 15 wherein A is selected from Het2 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

17. A pharmaceutical composition according to claim 16 wherein A is selected from Het3 optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

18. A pharmaceutical composition according to claim 17 wherein A is selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thienyl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

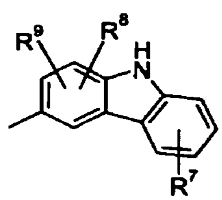
19. A pharmaceutical composition according to claim 17 wherein A is benzofuranyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

20. A pharmaceutical composition according to claim 19 wherein A is



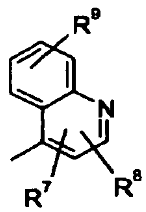
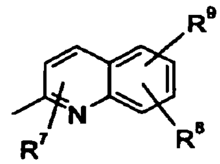
21. A pharmaceutical composition according to claim 17 wherein A is carbazolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

22. A pharmaceutical composition according to claim 21 wherein A is



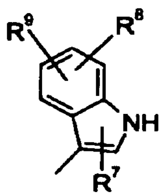
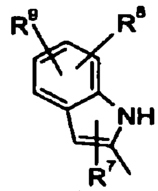
23. A pharmaceutical composition according to claim 17 wherein A is quinolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

24. A pharmaceutical composition according to claim 23 wherein A is

 or 

25. A pharmaceutical composition according to claim 17 wherein A is indolyl optionally substituted with up to four substituents R^7, R^8, R^9, and R^{10} which may be the same or different.

26. A pharmaceutical composition according to claim 25 wherein A is

 or 

27. A pharmaceutical composition according to any one of the claims 2 to 26 wherein R^1 is hydrogen.

28. A pharmaceutical composition according to any one of the claims 2 to 27 wherein R^2 is hydrogen.

29. A pharmaceutical composition according to any one of the claims 2 to 26 wherein R^1 and R^2 are combined to form a double bond.

30. A pharmaceutical composition according to any one of the claims 2 to 29 wherein R^3 is C_1-C_6-alkyl, halogen, or $C(O)NR^{16}R^{17}$.

31. A pharmaceutical composition according to claim 30 wherein R^3 is C_1-C_6-alkyl or $C(O)NR^{16}R^{17}$.

32. A pharmaceutical composition according to claim 31 wherein R^3 is methyl.

33. A pharmaceutical composition according to any one of the claims 2 to 8 wherein B is phenyl optionally substituted with up to four substituents, R^7, R^8, R^9, and R^{10} which may be the same or different.

34. A pharmaceutical composition according to any one of the claims 2 to 8 or 33 wherein R^4 is hydrogen.

35. A pharmaceutical composition according to any one of the claims 2 to 8 or 33 to 34 wherein R^5 is hydrogen.

36. A pharmaceutical composition according to any one of the claims 2 to 35 wherein R^6 is aryl.

37. A pharmaceutical composition according to claim 36 wherein R^6 is phenyl.

38. A pharmaceutical composition according to any one of the claims 2 to 37 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)_2NR^{11}R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2$ R^{11}, $-NR^{11}C(O)R^{12}$, $-CH_2OR^{11}$, $-CH_2OC(O)R^{11}$, $-CH_2NR^{11}R^{12}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)NR^{11}R^{12}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

39. A pharmaceutical composition according to claim 38 wherein R^7, R^8, R^9 and R^{10} are independently selected from

- hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2$ R^{11}, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

- C_1-C_6-alkyl or C_1-C_6-alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}

40. A pharmaceutical composition according to claim 39 wherein R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, $-NO_2$, $-OR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(O)_2R^{11}$, $-OS(O)_2 R^{11}$, $-CH_2OC(O)R^{11}$, $-OC(O)R^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, $-OC_1$-C_6-alkyl-OR^{11}, $-SC_1$-C_6-alkyl-$C(O)OR^{11}$, $-C(O)OR^{11}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{11}$,

• C_1-C_6-alkyl or C_1-C_6- which may each optionally be substituted with one or more substituents independently selected from R^{13}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

41. A pharmaceutical composition according to claim 40 wherein R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

• C_1-C_6-alkyl which may each optionally be substituted with one or more substituents independently selected from R^{13}

• aryl, aryloxy, aryl-C_1-C_6-alkoxy,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

42. A pharmaceutical composition according to claim 41 wherein R^7, R^8, R^9 and R^{10} are independently selected from

• hydrogen, halogen, $-OR^{11}$, $-OC_1$-C_6-alkyl-$C(O)OR^{11}$, or $-C(O)OR^{11}$,

• C_1-C_6-alkyl which may optionally be substituted with one or more substituents independently selected from R^{13}

• phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{14}.

43. A pharmaceutical composition according to any one of the claims 2 to 42 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}; R^{11} and R^{12} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds.

44. A pharmaceutical composition according to claim 43 wherein R^{11} and R^{12} are independently selected from hydrogen, C_1-C_{20}-alkyl, aryl or aryl-C_1-C_6-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R^{15}, and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16}.

45. A pharmaceutical composition according to claim 44 wherein R^{11} and R^{12} are independently selected from phenyl or phenyl-C_1-C_6-alkyl.

46. A pharmaceutical composition according to claim 44 wherein one or both of R^{11} and R^{12} are methyl.

47. A pharmaceutical composition according to any one of the claims 2 to 46 wherein R^{13} is independently selected from halogen, CF_3, OR^{11} or $NR^{11}R^{12}$.

48. A pharmaceutical composition according to claim 47 wherein R^{13} is independently selected from halogen or OR^{11}.

49. A pharmaceutical composition according to claim 48 wherein R^{13} is OR^{11}.

50. A pharmaceutical composition according to any one of the claims 2 to 49 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, -CN, -CF_3, -OR^{11}, $S(O)_2R^{11}$, and C_1-C_6-alkyl.

51. A pharmaceutical composition according to claim 50 wherein R^{14} is independently selected from halogen, -C(O)OR^{11}, or -OR^{11}.

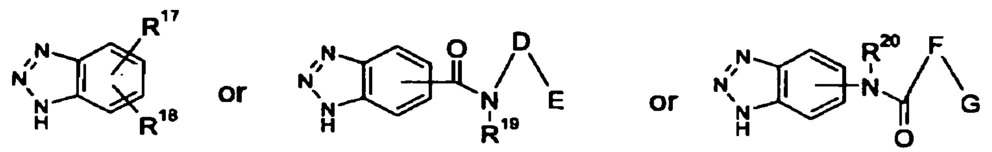
52. A pharmaceutical composition according to any one of the claims 2 to 51 wherein R^{15} is independently selected from halogen, -CN, -CF_3, -C(O)OC_1-C_6-alkyl,and –COOH.

53. A pharmaceutical composition according to claim 52 wherein R^{15} is independently selected from halogen or -C(O)OC_1-C_6-alkyl.

54. A pharmaceutical composition according to any one of the claims 2 to 53 wherein R^{16} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -NO_2, -OC_1-C_6-alkyl, -NH_2, C(=O) or C_1-C_6-alkyl.

55. A pharmaceutical composition according to claim 54 wherein R^{16} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, $-NO_2$, or C_1-C_6-alkyl.

56. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is



wherein

R^{19} is hydrogen or C_1-C_6-alkyl,

R^{20} is hydrogen or C_1-C_6-alkyl,

D and F are a valence bond or C_1-C_6-alkylene optionally substituted with one or more substituents independently selected from R^{72},

R^{72} is independently selected from hydroxy, C_1-C_6-alkyl, or aryl,

E is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{21}, R^{22} and R^{23},

G is C_1-C_6-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26},

R^{17}, R^{18}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}S(O)_2R^{28}$, $-S(O)_2NR^{27}R^{28}$, $-S(O)NR^{27}R^{28}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29},

• aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30},

R^{27} and R^{28} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{27} and R^{28} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{29} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{27}$, and $-NR^{27}R^{28}$,

R^{30} is independently selected from halogen, $-C(O)OR^{27}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$ and C_1-C_6-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

57. A pharmaceutical composition according to claim 56 wherein D is a valence bond.

58. A pharmaceutical composition according to claim 56 wherein D is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

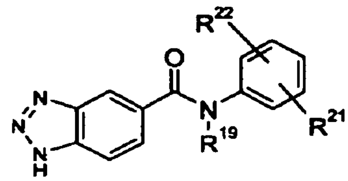
59. A pharmaceutical composition according to any one of the claims 56 to 58 wherein E is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

60. A pharmaceutical composition according to claim 59 wherein E is aryl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

61. A pharmaceutical composition according to claim 60 wherein E is selected from ArG1 and optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

62. A pharmaceutical composition according to claim 61 wherein E is phenyl optionally substituted with up to three substituents independently selected from R^{21}, R^{22} and R^{23}.

63. A pharmaceutical composition according to claim 62 wherein the zinc-binding ligand is



64. A pharmaceutical composition according to any one of the claims 56 to 63 wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

65. A pharmaceutical composition according to claim 64 wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-

C(=O)OR^{27}, -C(=O)NR^{27}-C$_1$-C$_6$-alkyl-C(=O)OR^{27}, -C$_1$-C$_6$-alkyl-C(=O)OR^{27}, or -C(O)OR^{27},

• C$_1$-C$_6$-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C$_1$-C$_6$-alkoxy, aryl-C$_1$-C$_6$-alkyl, heteroaryl, heteroaryl-C$_1$-C$_6$-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

66. A pharmaceutical composition according to claim 65 wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, -OCF$_3$, -OR^{27}, -NR^{27}R^{28}, -SR^{27}, -NR^{27}C(O)R^{28}, -NR^{27}C(O)OR^{28}, -OC(O)R^{27}, -OC$_1$-C$_6$-alkyl-C(O)OR^{27}, -SC$_1$-C$_6$-alkyl-C(O)OR^{27}, –C$_2$-C$_6$-alkenyl-C(=O)OR^{27}, -C(=O)NR^{27}-C$_1$-C$_6$-alkyl-C(=O)OR^{27}, -C$_1$-C$_6$-alkyl-C(=O)OR^{27}, or -C(O)OR^{27},

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C$_1$-C$_6$-alkoxy, aryl-C$_1$-C$_6$-alkyl, heteroaryl, heteroaryl-C$_1$-C$_6$-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

67. A pharmaceutical composition according to claim 66 wherein R^{21}, R^{22} and R^{23} are independently selected from

• hydrogen, halogen, -OCF$_3$, -OR^{27}, -NR^{27}R^{28}, -SR^{27}, -NR^{27}C(O)R^{28}, -NR^{27}C(O)OR^{28}, -OC(O)R^{27}, -OC$_1$-C$_6$-alkyl-C(O)OR^{27}, -SC$_1$-C$_6$-alkyl-C(O)OR^{27}, –C$_2$-C$_6$-alkenyl-C(=O)OR^{27}, -C(=O)NR^{27}-C$_1$-C$_6$-alkyl-C(=O)OR^{27}, -C$_1$-C$_6$-alkyl-C(=O)OR^{27}, or -C(O)OR^{27},

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

68. A pharmaceutical composition according to claim 67 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, -OCF_3, -OR^{27}, -$NR^{27}R^{28}$, -SR^{27}, -$NR^{27}C(O)R^{28}$, -$NR^{27}C(O)OR^{28}$, -$OC(O)R^{27}$, -OC_1-C_6-alkyl-$C(O)OR^{27}$, -SC_1-C_6-alkyl-$C(O)OR^{27}$, -C_2-C_6-alkenyl-$C(=O)OR^{27}$, -$C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, -C_1-C_6-alkyl-$C(=O)OR^{27}$, or -$C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

69. A pharmaceutical composition according to any one of the claims 56 to 68 wherein R^{19} is hydrogen or methyl.

70. A pharmaceutical composition according to claim 69 wherein R^{19} is hydrogen.

71. A pharmaceutical composition according to any one of the claims 56 to 70 wherein R^{27} is Hydrogen, C_1-C_6-alkyl or aryl.

72. A pharmaceutical composition according to claim 71 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

73. A pharmaceutical composition according to any one of the claims 56 to 72 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

74. A pharmaceutical composition according to claim 56 wherein F is a valence bond.

75. A pharmaceutical composition according to claim 56 wherein F is C_1-C_6-alkylene optionally substituted with one or more hydroxy, C_1-C_6-alkyl, or aryl.

76. A pharmaceutical composition according to any one of the claims 56 or 74 to 75 wherein G is C_1-C_6-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

77. A pharmaceutical composition according to any one of the claims 56 or 74 to 75 wherein G is C_1-C_6-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

78. A pharmaceutical composition according to claim 76 wherein G is C_1-C_6-alkyl.

79. A pharmaceutical composition according to claim 78 wherein G is phenyl optionally substituted with up to three substituents R^{24}, R^{25} and R^{26}.

80. A pharmaceutical composition according to any one of the claims 56 to 79 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-C(O)NR^{27}R^{28}$, $-OC(O)NR^{27}R^{28}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-CH_2C(O)NR^{27}R^{28}$, $-OCH_2C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-CH_2NR^{27}R^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-NR^{27}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{27}$-, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

81. A pharmaceutical composition according to claim 80 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

which may optionally be substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

82. A pharmaceutical composition according to claim 81 wherein R^{24}, R^{25} and R^{26} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

- aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

83. A pharmaceutical composition according to claim 82 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

84. A pharmaceutical composition according to claim 83 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{27}$, $-C(=O)NR^{27}$-C_1-C_6-alkyl-$C(=O)OR^{27}$, $-C_1$-C_6-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

85. A pharmaceutical composition according to claim 84 wherein R^{21}, R^{22} and R^{23} are independently selected from

- hydrogen, halogen, $-OCF_3$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-NR^{27}C(O)R^{28}$, $-NR^{27}C(O)OR^{28}$, $-OC(O)R^{27}$, $-OC_1$-C_6-alkyl-$C(O)OR^{27}$, $-SC_1$-C_6-alkyl-$C(O)OR^{27}$, $-C_2$-C_6-alkenyl-

$C(=O)OR^{27}$, $-C(=O)NR^{27}-C_1-C_6$-alkyl-$C(=O)OR^{27}$, $-C_1-C_6$-alkyl-$C(=O)OR^{27}$, or $-C(O)OR^{27}$,

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

86. A pharmaceutical composition according to any one of the claims 56 or 74 to 85 wherein R^{20} is hydrogen or methyl.

87. A pharmaceutical composition according to claim 86 wherein R^{20} is hydrogen.

88. A pharmaceutical composition according to any one of the claims 56 or 74 to 87 wherein R^{27} is hydrogen, C_1-C_6-alkyl or aryl.

89. A pharmaceutical composition according to claim 88 wherein R^{27} is hydrogen or C_1-C_6-alkyl or ArG1.

90. A pharmaceutical composition according to claim 89 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

91. A pharmaceutical composition according to any one of the claims 56 or 74 to 89 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

92. A pharmaceutical composition according to claim 56 wherein R^{17} and R^{18} are independently selected from

• hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, $-SR^{27}$, $-S(O)R^{27}$, $-S(O)_2R^{27}$, $-C(O)NR^{27}R^{28}$, $-CH_2OR^{27}$, $-OC(O)R^{27}$, $-OC_1-C_6$-alkyl-$C(O)OR^{27}$, $-SC_1-C_6$-alkyl-$C(O)OR^{27}$, or $-C(O)OR^{27}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

93. A pharmaceutical composition according to claim 92 wherein R^{17} and R^{18} are independently selected from

• hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$,

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

94. A pharmaceutical composition according to claim 93 wherein R^{17} and R^{18} are independently selected from

• hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• aryl, aryloxy, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

95. A pharmaceutical composition according to claim 94 wherein R^{17} and R^{18} are independently selected from

• hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$

• methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R^{29}

• ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, Het3, Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

96. A pharmaceutical composition according to claim 95 wherein R^{17} and R^{18} are independently selected from

• hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{27}$, $-NR^{27}R^{28}$, or $-C(O)OR^{27}$

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{29}

• phenyl, phenyloxy, phenyl-C_1-C_6-alkoxy, phenyl-C_1-C_6-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{30}.

97. A pharmaceutical composition according to any one of the claims 56 to 96 wherein R^{27} is hydrogen or C_1-C_6-alkyl.

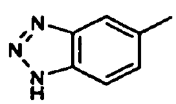
98. A pharmaceutical composition according to claim 97 wherein R^{27} is hydrogen, methyl or ethyl.

99. A pharmaceutical composition according to any one of the claims 56 to 98 wherein R^{28} is hydrogen or C_1-C_6-alkyl.

100. A pharmaceutical composition according to claim 99 wherein R^{28} is hydrogen, methyl or ethyl.

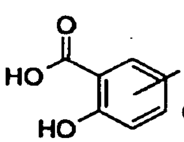
101. A pharmaceutical composition according to any one of the claims 56 to 100 wherein R^{72} is –OH or phenyl.

102. A pharmaceutical composition according to claim 56 wherein the zinc-binding ligand is

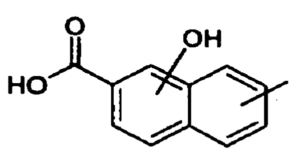


103. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is of the form H-I-J

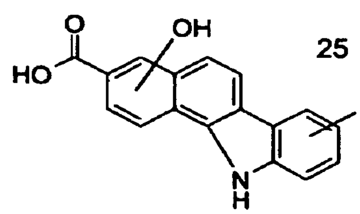
wherein H is



or

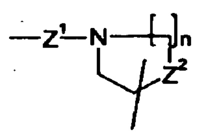


or



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31}

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is -NH-, -O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- Hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

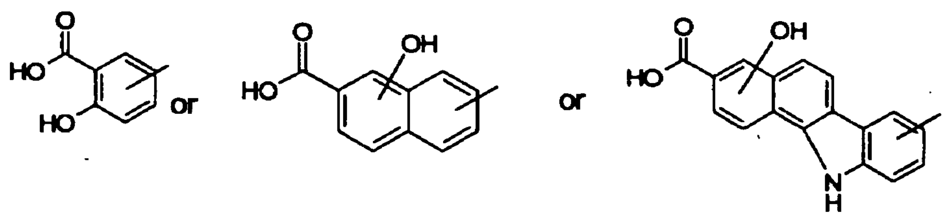
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{37} is independently selected from halogen, -C(O)OR^{35}, -C(O)H, -CN, -CF_3, -OCF_3, -NO_2, -OR^{35}, -NR^{35}R^{38}, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

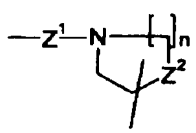
or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

104. A pharmaceutical composition according to claim 103 wherein the zinc-binding ligand is of the form H-I-J, wherein H is



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R^{31},

I is selected from

- a valence bond,
- –$CH_2N(R^{32})$- or –$SO_2N(R^{33})$-,
-  wherein Z^1 is $S(O)_2$ or CH_2, Z^2 is N,-O-or -S-, and n is 1 or 2,

J is

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34},
- Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl-C_1-C_6-alkoxy-, aryl-C_1-C_6-alkyl-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroaryl, heteroaryl-C_1-C_6-alkyl-, heteroaryl-C_2-C_6-alkenyl- or heteroaryl-C_2-C_6-alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37},
- hydrogen,

R^{31} is independently selected from hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -SCF_3, -NO_2, -OR^{35}, -C(O)R^{35}, -NR^{35}R^{38}, -SR^{35},

$-NR^{35}S(O)_2R^{36}$, $-S(O)_2NR^{35}R^{36}$, $-S(O)NR^{35}R^{36}$, $-S(O)R^{35}$, $-S(O)_2R^{35}$, $-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-CH_2C(O)NR^{35}R^{36}$, $-OCH_2C(O)NR^{35}R^{36}$, $-CH_2OR^{35}$, $-CH_2NR^{35}R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ $-C_2$-C_6-alkenyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{35}$, $-NR^{35}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{35}$-, C_1-C_6-alkyl, C_1-C_6-alkanoyl or $-C(O)OR^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

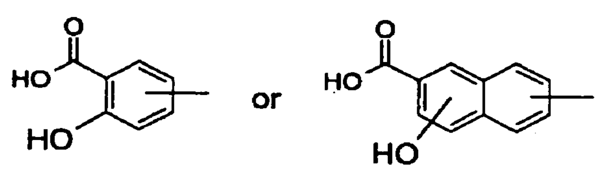
R^{34} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,

R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, aryl-C_1-C_6-alkyl or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

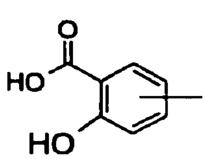
R^{37} is independently selected from halogen, $-C(O)OR^{35}$, -C(O)H, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base,
With the proviso that R^{31} and J cannot both be hydrogen.

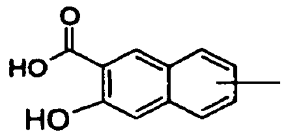
105. A pharmaceutical composition according to any one of the claims 103 or 104 wherein H is



106. A pharmaceutical composition according to claim 105 wherein H is



107. A pharmaceutical composition according to claim 105 wherein H is



108. A pharmaceutical composition according to any one of the claims 103 to 107wherein I is a valence bond, $-CH_2N(R^{32})-$, or $-SO_2N(R^{33})-$.

109. A pharmaceutical composition according to claim 108 wherein I is a valence bond.

110. A pharmaceutical composition according to any one of the claims 103 to 109 wherein J is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{35}$, and $-NR^{35}R^{36}$,
- aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

111. A pharmaceutical composition according to claim 110 wherein J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

112. A pharmaceutical composition according to claim 110 wherein J is

- hydrogen,
- ArG1 or Het3, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37}.

113. A pharmaceutical composition according to claim 112 wherein J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37}.

114. A pharmaceutical composition according to claim 113 wherein J is hydrogen.

115. A pharmaceutical composition according to any one of the claims 103 to 114 wherein R^{32} and R^{33} are independently selected from hydrogen or C_1-C_6-alkyl.

116. A pharmaceutical composition according to any one of the claims 103 to 115 wherein R^{34} is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$,

$-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OC(O)R^{35}$, $-OC_1$-C_6-alkyl-$C(O)OR^{35}$, $-SC_1$-C_6-alkyl-$C(O)OR^{35}$ or $-C(O)OR^{35}$.

117. A pharmaceutical composition according to claim 116 wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}C(O)R^{36}$, or $-C(O)OR^{35}$.

118. A pharmaceutical composition according to claim 117 wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, or $-NR^{35}C(O)R^{36}$.

119. A pharmaceutical composition according to claim 118 wherein R^{34} is hydrogen, halogen, or $-OR^{35}$.

120. A pharmaceutical composition according to any one of the claims 103 to 119 wherein R^{35} and R^{36} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl.

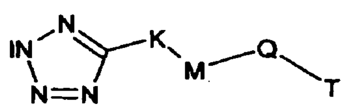
121. A pharmaceutical composition according to claim 120 wherein R^{35} and R^{36} are independently selected from hydrogen or C_1-C_6-alkyl.

122. A pharmaceutical composition according to any one of the claims 103 to 121 wherein R^{37} is halogen, $-C(O)OR^{35}$, -CN, $-CF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

123. A pharmaceutical composition according to claim 122 wherein R^{37} is halogen, -$C(O)OR^{35}$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6-alkyl or C_1-C_6-alkanoyl.

124. A pharmaceutical composition according to claim 123 wherein R^{37} is halogen, -$C(O)OR^{35}$ or $-OR^{35}$.

125. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is



wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, $-C_1$-C_6-alkyl-S-, $-C_1$-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38},

U is a valence bond, C_1-C_6-alkenylene, $-C_1$-C_6-alkyl-O- or C_1-C_6-alkylene wherein any C_1-C_6-alkyl moiety is optionally substituted with C_1-C_6-alkyl,

R^{38} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39},

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{40},

R^{40} is selected from

- hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-NR^{41}S(O)_2R^{42}$, $-S(O)_2NR^{41}R^{42}$, $-S(O)NR^{41}R^{42}$, $-S(O)R^{41}$, $-S(O)_2R^{41}$, $-OS(O)_2$ R^{41}, $-C(O)NR^{41}R^{42}$, $-OC(O)NR^{41}R^{42}$, $-NR^{41}C(O)R^{42}$, $-CH_2C(O)NR^{41}R^{42}$, $-OC_1-C_6$-alkyl-$C(O)NR^{41}R^{42}$, $-CH_2OR^{41}$, $-CH_2OC(O)R^{41}$, $-CH_2NR^{41}R^{42}$, $-OC(O)R^{41}$, $-OC_1-C_6$-alkyl-$C(O)OR^{41}$, $-OC_1-C_6$-alkyl-OR^{41}, $-S-C_1-C_6$-alkyl-$C(O)OR^{41}$, $-C_2-C_6$-alkenyl-$C(=O)OR^{41}$, $-NR^{41}-C(=O)-C_1-C_6$-alkyl-$C(=O)OR^{41}$, $-NR^{41}-C(=O)-C_1-C_6$-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, $-C_2-C_6$-alkenyl-$C(=O)R^{41}$, =O, $-NH-C(=O)-O-C_1-C_6$-alkyl, or $-NH-C(=O)-C(=O)-O-C_1-C_6$-alkyl,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may each optionally be substituted with one or more substituents selected from R^{43},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44},

R^{41} and R^{42} are independently selected from hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R^{45}, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R^{46}; R^{41} and R^{42} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{43} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{41}$, and $-NR^{41}R^{42}$

R^{44} is independently selected from halogen, $-C(O)OR^{41}$, $-CH_2C(O)OR^{41}$, $-CH_2OR^{41}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$ and C_1-C_6-alkyl,

R^{45} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl, -COOH and $-NH_2$,

R^{46} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, -OC_1-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48},

R^{47} and R^{48} are independently selected from hydrogen, C_1-C_6-alkyl, aryl optionally substituted with one or more R^{49},

R^{49} is independently selected from halogen and –COOH,

T is

- hydrogen,
- C_1-C_6-alkyl, C_2-C_6-alkenyl , C_2-C_6-alkynyl, C_1-C_6-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R^{50},
- aryl, aryloxy, aryloxy-carbonyl, aryl-C_1-C_6-alkyl, aroyl, aryl-C_1-C_6-alkoxy, aryl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkyny-, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl, heteroaryl-C_2-C_6-alkynyl,

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{50},

R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, $-S(O)_2R^{51}$, -C_2-C_6-alkenyl-COOH, $-OR^{51}$, $-NO_2$, halogen, -COOH, $-CF_3$, -CN, =O, $-N(R^{51}R^{52})$, wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53},

R^{51} and R^{52} are independently selected from hydrogen and C_1-C_6-alkyl,

R^{53} is independently selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, or -N($R^{51}R^{52}$),

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

126. A pharmaceutical composition according to claim 125 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, or -C(=O)-, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

127. A pharmaceutical composition according to claim 126 wherein K is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-U-, -C_1-C_6-alkyl-S-, or -C_1-C_6-alkyl-O, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

128. A pharmaceutical composition according to claim 127 wherein K is a valence bond, C_1-C_6-alkylene, or -NH-C(=O)-U, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

129. A pharmaceutical composition according to claim 128 wherein K is a valence bond or C_1-C_6-alkylene, wherein any C_1-C_6-alkyl moiety is optionally substituted with R^{38}.

130. A pharmaceutical composition according to claim 128 wherein K is a valence bond or -NH-C(=O)-U.

131. A pharmaceutical composition according to claim 129 wherein K is a valence bond.

132. A pharmaceutical composition according to any one of the claims 125 to 131 wherein U is a valence bond or -C_1-C_6-alkyl-O-.

133. A pharmaceutical composition according to claim 132 wherein U is a valence bond

134. A pharmaceutical composition according to any one of the claims 125 to 133 wherein M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

135. A pharmaceutical composition according to claim 134 wherein M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

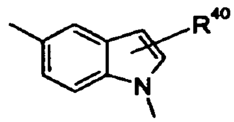
136. A pharmaceutical composition according to claim 135 wherein M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

137. A pharmaceutical composition according to claim 136 wherein M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R^{40}.

138. A pharmaceutical composition according to claim 137 wherein M is phenylene optionally substituted with one or more substituents independently selected from R^{40}.

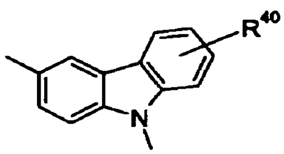
139. A pharmaceutical composition according to claim 137 wherein M is indolylene optionally substituted with one or more substituents independently selected from R^{40}.

140. A pharmaceutical composition according to claim 139 wherein M is



141. A pharmaceutical composition according to claim 137 wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R^{40}.

142. A pharmaceutical composition according to claim 141 wherein M is



143. A pharmaceutical composition according to any one of the claims 125 to 142 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1-C_6$-alkyl-$C(O)NR^{41}R^{42}$, $-C_2-C_6$-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

- aryl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, or heteroaryl-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

144. A pharmaceutical composition according to claim 143 wherein R^{40} is selected from

- hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{41}$, $-NR^{41}R^{42}$, $-SR^{41}$, $-S(O)_2R^{41}$, $-NR^{41}C(O)R^{42}$, $-OC_1-C_6$-alkyl-$C(O)NR^{41}R^{42}$, $-C_2-C_6$-alkenyl-$C(=O)OR^{41}$, $-C(O)OR^{41}$, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)-O-C_1-C_6-alkyl,

  C_1-C_6-alkyl or C_2-C_6- alkenyl which may each optionally be substituted with one or more substituents independently selected from R^{43},

• ArG1, ArG1-O-, ArG1-C_1-C_6-alkoxy, ArG1-C_1-C_6-alkyl, ArG1-C_2-C_6-alkenyl, Het3, Het3-C_1-C_6-alkyl, or Het3-C_2-C_6-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R^{44}.

145. A pharmaceutical composition according to claim 144 wherein R^{40} is selected from

• hydrogen, halogen, -CF_3, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -C(O)OR^{41}, =O, or -$NR^{41}C(O)R^{42}$,

• C_1-C_6-alkyl,

• ArG1.

146. A pharmaceutical composition according to claim 145 wherein R^{40} is selected from

• Halogen, -NO_2, -OR^{41}, -$NR^{41}R^{42}$, -C(O)OR^{41}, or -$NR^{41}C(O)R^{42}$,

• Methyl,

• Phenyl.

147. A pharmaceutical composition according to any one of the claims 125 to 146 wherein R^{41} and R^{42} are independently selected from hydrogen, C_1-C_6-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

148. A pharmaceutical composition according to claim 147 wherein R^{41} and R^{42} are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

149. A pharmaceutical composition according to any one of the claims 125 to 148 wherein Q is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^{47})- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R^{48}.

150. A pharmaceutical composition according to claim 149 wherein Q is a valence bond, -CH_2-, -CH_2-CH_2-, -CH_2-O-, -CH_2-CH_2-O-, -CH_2-NH-, -CH_2-CH_2-NH-, -NH-CH_2-, -NH-CH_2-CH_2-, -NH-C(=O)-, -C(=O)-NH-, -O-CH_2-, -O-CH_2-CH_2-, or -C(=O)-.

151. A pharmaceutical composition according to any one of the claims 125 to 150 wherein R^{47} and R^{48} are independently selected from hydrogen, methyl and phenyl.

152. A pharmaceutical composition according to any one of the claims 125 to 151 wherein T is

• Hydrogen,

• C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},

• aryl, aryl-C_1-C_6-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

153. A pharmaceutical composition according to claim 152 wherein T is

- hydrogen,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{50},
- ArG1, ArG1-C_1-C_6-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

154. A pharmaceutical composition according to claim 153 wherein T is

- hydrogen,
- C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from R^{50},
- phenyl, phenyl-C_1-C_6-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R^{50}.

155. A pharmaceutical composition according to any one of the claims 125 to 154 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-C_1-C_6-alkyl-aryl, heteroaryl, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -S(O)$_2$R^{51}, -C_2-C_6-alkenyl-COOH, -OR^{51}, -NO_2, halogen, -COOH, -CF_3, -CN, =O, -N($R^{51}R^{52}$), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53}.

156. A pharmaceutical composition according to claim 155 wherein R^{50} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy , -OR^{51}, -NO_2, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

157. A pharmaceutical composition according to claim 156 wherein R^{50} is C_1-C_6-alkyl, aryloxy, aryl-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

158. A pharmaceutical composition according to claim 157 wherein R^{50} is C_1-C_6-alkyl, ArG1-O-, ArG1-C_1-C_6-alkoxy , -OR^{51}, halogen, -COOH, -CF_3, wherein any aryl moiety is optionally substituted with one or more R^{53}.

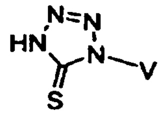
159. A pharmaceutical composition according to claim 158 wherein R^{50} is phenyl, methyl or ethyl.

160. A pharmaceutical composition according to claim 159 wherein R^{50} is methyl or ethyl.

161. A pharmaceutical composition according to any one of the claims 125 to 160 wherein R^{51} is methyl.

162. A pharmaceutical composition according to any one of the claims 125 to 161 wherein R^{53} is C_1-C_6-alkyl, C_1-C_6-alkoxy, -OR^{51}, halogen,or -CF_3.

163. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is



wherein V is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55},

R^{54} is independently selected from halogen, -CN, -CF_3, -OCF_3, aryl, -COOH and –NH_2,
R^{55} is independently selected from

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -SR^{56}, -$NR^{56}S(O)_2R^{57}$, -$S(O)_2NR^{56}R^{57}$, -$S(O)NR^{56}R^{57}$, -$S(O)R^{56}$, -$S(O)_2R^{56}$, -$OS(O)_2$ R^{56}, -$C(O)NR^{56}R^{57}$, -$OC(O)NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$, -$CH_2C(O)NR^{56}R^{57}$, -OC_1-C_6-alkyl-$C(O)NR^{56}R^{57}$, -CH_2OR^{56}, -$CH_2OC(O)R^{56}$, -$CH_2NR^{56}R^{57}$, -$OC(O)R^{56}$, -OC_1-C_6-alkyl-$C(O)OR^{56}$, -OC_1-C_6-alkyl-OR^{56}, -SC_1-C_6-alkyl-$C(O)OR^{56}$, –C_2-C_6-alkenyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkyl-$C(=O)OR^{56}$, -NR^{56}-C(=O)-C_1-C_6-alkenyl-$C(=O)OR^{56}$, -$C(O)OR^{56}$, or –C_2-C_6-alkenyl-$C(=O)R^{56}$,

- C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl,

  which may optionally be substituted with one or more substituents selected from R^{58},

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{59},

R^{56} and R^{57} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, -C(=O)-C_1-C_6-alkyl or aryl, wherein the alkyl groups may optionally be substituted with

one or more substituents independently selected from R^{60}, and the aryl groups may optionally be substituted with one or more substituents independently selected from R^{61}; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{58} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{56}$, and $-NR^{56}R^{57}$,

R^{59} is independently selected from halogen, $-C(O)OR^{56}$, $-CH_2C(O)OR^{56}$, $-CH_2OR^{56}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{56}$, $-NR^{56}R^{57}$ and C_1-C_6-alkyl,

R^{60} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, $-C(O)OC_1$-C_6-alkyl, $-C(=O)-R^{62}$, -COOH and $-NH_2$,

R^{61} is independently selected from halogen, $-C(O)OC_1$-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

R^{62} is C_1-C_6-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl independently,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

164. A pharmaceutical composition according to claim 163 wherein V is aryl, heteroaryl, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R^{54}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55}.

165. A pharmaceutical composition according to claim 164 wherein V is aryl, Het1, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

166. A pharmaceutical composition according to claim 165 wherein V is aryl, Het2, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents

independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

167. A pharmaceutical composition according to claim 166 wherein V is aryl, Het3, or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R^{54}, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R^{55}.

168. A pharmaceutical composition according to claim 167 wherein V is aryl optionally substituted with one or more substituents independently selected from R^{55}.

169. A pharmaceutical composition according to claim 168 wherein V is ArG1 optionally substituted with one or more substituents independently selected from R^{55}.

170. A pharmaceutical composition according to claim 169 wherein V is phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R^{55}.

171. A pharmaceutical composition according to claim 170 wherein V is phenyl optionally substituted with one or more substituents independently selected from R^{55}.

172. A pharmaceutical composition according to any one of the claims 163 to 171 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_6-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$,
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- aryl, aryl-C_1-C_6-alkyl, heteroaryl, or heteroaryl-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

173. A pharmaceutical composition according to claim 172 wherein R^{55} is independently selected from

- halogen, C_1-C_6-alkyl, -CN, -OCF_3 ,-CF_3, -NO_2, -OR^{56}, -$NR^{56}R^{57}$, -$NR^{56}C(O)R^{57}$ -SR^{56}, -OC_1-C_6-alkyl-$C(O)OR^{56}$, or -$C(O)OR^{56}$
- C_1-C_6-alkyl optionally substituted with one or more substituents independently selected from R^{58}
- ArG1, ArG1-C_1-C_6-alkyl, Het3, or Het3-C_1-C_6-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R^{59}.

174. A pharmaceutical composition according to claim 173 wherein R^{55} is independently selected from halogen, $-OR^{56}$, $-NR^{56}R^{57}$, $-C(O)OR^{56}$, $-OC_1-C_8\text{-alkyl-}C(O)OR^{56}$, $-NR^{56}C(O)R^{57}$ or C_1-C_8-alkyl.

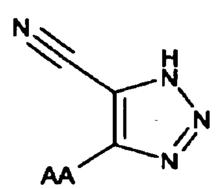
175. A pharmaceutical composition according to claim 174 wherein R^{55} is independently selected from halogen, $-OR^{56}$, $-NR^{56}R^{57}$, $-C(O)OR^{56}$, $-OC_1-C_8\text{-alkyl-}C(O)OR^{56}$, $-NR^{56}C(O)R^{57}$, methyl or ethyl.

176. A pharmaceutical composition according to any one of the claims 163 to 175 wherein R^{56} and R^{57} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, or $-C(=O)-C_1-C_8$-alkyl; R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

177. A pharmaceutical composition according to claim 176 wherein R^{56} and R^{57} are independently selected from hydrogen or C_1-C_{12}-alkyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

178. A pharmaceutical composition according to claim 177 wherein R^{56} and R^{57} are independently selected from hydrogen or methyl, ethyl, propyl butyl, R^{56} and R^{57} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

179. A pharmaceutical composition according to claim 1 wherein the zinc-binding ligand is



wherein AA is C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl- or aryl-C_{2-6}-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64},

R^{63} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, aryl, -COOH and $-NH_2$,

R^{64} is independently selected from

• hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$, $-SR^{65}$, $-NR^{65}S(O)_2R^{66}$, $-S(O)_2NR^{65}R^{66}$, $-S(O)NR^{65}R^{66}$, $-S(O)R^{65}$, $-S(O)_2R^{65}$, $-OS(O)_2$ R^{65}, $-C(O)NR^{65}R^{66}$, $-OC(O)NR^{65}R^{66}$, $-NR^{65}C(O)R^{66}$, $-CH_2C(O)NR^{65}R^{66}$, $-OC_1$-C_6-alkyl-$C(O)NR^{65}R^{66}$, $-CH_2OR^{65}$, $-CH_2OC(O)R^{65}$, $-CH_2NR^{65}R^{66}$, $-OC(O)R^{65}$, $-OC_1$-C_6-alkyl-$C(O)OR^{65}$, $-OC_1$-C_6-alkyl-OR^{65}, $-SC_1$-C_6-alkyl-$C(O)OR^{65}$, $-C_2$-C_6-alkenyl-$C(=O)OR^{65}$, $-NR^{65}$-$C(=O)$-C_1-C_6-alkyl-$C(=O)OR^{65}$, $-NR^{65}$-$C(=O)$-C_1-C_6-alkenyl-$C(=O)OR^{65}$, $-C(O)OR^{65}$, or $-C_2$-C_6-alkenyl-$C(=O)R^{65}$,

• C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, each of which may optionally be substituted with one or more substituents selected from R^{67},

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{68},

R^{65} and R^{66} are independently selected from hydrogen, OH, CF_3, C_1-C_{12}-alkyl, aryl-C_1-C_6-alkyl, $-C(=O)$-R^{69}, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted with one or more substituents selected from R^{70}, and the aryl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from R^{71}; R^{65} and R^{66} when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{67} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{65}$, and $-NR^{65}R^{66}$,

R^{68} is independently selected from halogen, $-C(O)OR^{65}$, $-CH_2C(O)OR^{65}$, $-CH_2OR^{65}$, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{65}$, $-NR^{65}R^{66}$ and C_1-C_6-alkyl,

R^{69} is independently selected from C_1-C_6-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C_1-C_6-alkyl,

R^{70} is independently selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OC_1$-C_6-alkyl, -C(O)OC_1-C_6-alkyl, -COOH and $-NH_2$,

R^{71} is independently selected from halogen, -C(O)OC_1-C_6-alkyl, -COOH, -CN, $-CF_3$, $-OCF_3$, -NO_2, -OH, $-OC_1$-C_6-alkyl, $-NH_2$, C(=O) or C_1-C_6-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

180. A pharmaceutical composition according to claim 179 wherein AA is aryl, heteroaryl or aryl-C_{1-6}-alkyl-, wherein the alkyl is optionally substituted with one or more R^{63}, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{64}.

181. A pharmaceutical composition according to claim 180 wherein AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected from R^{64}.

182. A pharmaceutical composition according to claim 181 wherein AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{64}.

183. A pharmaceutical composition according to claim 182 wherein AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{64}.

184. A pharmaceutical composition according to claim 183 wherein AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{64}.

185. A pharmaceutical composition according to claim 184 wherein AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R^{64}.

186. A pharmaceutical composition according to claim 185 wherein AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R^{64}.

187. A pharmaceutical composition according to any one of the claims 179 to 186 wherein R^{64} is independently selected from hydrogen, halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, C_1-C_6-alkyl , -OC(O)R^{65}, $-OC_1$-C_6-alkyl-C(O)OR^{65}, aryl-C_2-C_6-alkenyl, aryloxy or aryl, wherein C_1-C_6-alkyl is optionally substituted with one or more substituents independently selected from R^{67}, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R^{68}.

188. A pharmaceutical composition according to claim 187 wherein R^{64} is independently selected from halogen, $-CF_3$, $-OCF_3$, $-OR^{65}$, $-NR^{65}R^{66}$, methyl, ethyl, propyl, -OC(O)R^{65},

$-OCH_2-C(O)OR^{65}$, $-OCH_2-CH_2-C(O)OR^{65}$, phenoxy optionally substituted with one or more substituents independently selected from R^{68}.

189. A pharmaceutical composition according to any one of the claims 179 to 188 wherein R^{65} and R^{66} are independently selected from hydrogen, CF_3, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

190. A pharmaceutical composition according to claim 189 wherein R^{65} and R^{66} are independently hydrogen, C_1-C_{12}-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R^{71}.

191. A pharmaceutical composition according to claim 190 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R^{71}.

192. A pharmaceutical composition according to claim 191 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R^{71}.

193. A pharmaceutical composition according to claim 192 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R^{71}.

194. A pharmaceutical composition according to claim 193 wherein R^{65} and R^{66} are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R^{71} independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R^{71}.

195. A pharmaceutical composition according to any one of the claims 179 to 194 wherein R^{71} is halogen or C_1-C_6-alkyl.

196. A pharmaceutical composition according to claim 195 wherein R^{71} is halogen or methyl.

197. A pharmaceutical composition according to any one of the claims 1 to 196 wherein the insulin is rapid acting insulin.

198. A pharmaceutical composition according to any one of the claims 1 to 197 wherein the insulin is selected from the group consisting of human insulin, an analogue thereof, a derivative thereof, and combinations of any of these.

199. A pharmaceutical composition according to claim 198 wherein the insulin is an analogue of human insulin selected from the group consisting of

iii. An analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; and

iv. des(B28-B30), des(B27) or des(B30) human insulin.

200. A pharmaceutical composition according to claim 199, wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

201. A pharmaceutical composition according to claim 199 wherein the insulin is des(B30) human insulin.

202. A pharmaceutical composition according to claim 199 wherein the insulin is is an analogue of human insulin wherein position B3 is Lys and position B29 is Glu or Asp.

203. A pharmaceutical composition according to claim 198 wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

204. A pharmaceutical composition according to claim 203 wherein the insulin derivative is selected from the group consisting of B29-N^{ε}-myristoyl-des(B30) human insulin, B29-N^{ε}-palmitoyl-des(B30) human insulin, B29-N^{ε}-myristoyl human insulin, B29-N^{ε}-palmitoyl human insulin, B28-N^{ε}-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^{ε}-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^{ε}-myristoyl-$Thr^{B29}Lys^{B30}$ human insulin, B30-N^{ε}-palmitoyl-$Thr^{B29}Lys^{B30}$ human insulin, B29-N^{ε}-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^{ε}-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^{ε}-(ω-carboxyheptadecanoyl) human insulin.

205. A pharmaceutical composition according to claim 204 wherein the insulin derivative is B29-N^{ε}-myristoyl-des(B30) human insulin.

206. A pharmaceutical composition according to any one of the claims 1 to 205 further comprising at least 3 molecules of a phenolic compound per insulin hexamer.

207. A pharmaceutical composition according to any one of the claims 1 to 206 further comprising an isotonicity agent.

208. A pharmaceutical composition according to any one of the claims 1 to 207 further comprising a buffer substance.

209. A method of stabilising an insulin preparation comprising adding a zinc-binding ligand according to any one of the claims 1 to 196 to the insulin preparation.

210. A method of treating type 1 or type 2 diabetes comprising administering to a patient in need thereof a pharmaceutically effective dose of an insulin preparation according to any one of the claims 1 to196.

ABSTRACT

The present invention provides pharmaceutical preparations comprising insulin and novel ligands for the His^{B10} Zn^{2+} sites of the R-state insulin hexamer. The resulting preparations have improved physical and chemical stability.